isoform derives from a differential splicing pattern of the **FN** primary transcript which leads, in transformed cells, to a high level expression of the exon **ED-B** (Zardi, L., B. Carnemolla, A. Siri, T. E. Petersen, G. Paolella, G. Sebastio, and F. E. Baralle. 1987. EMBO (Eur. Mol. Biol. Organ.) J. 6:2337-2342). Here we report on the production and characterization of a monoclonal antibody (BC-1) which recognizes an epitope within the protein sequence coded for by the **ED-B** exon. This monoclonal antibody makes it possible to carry out immunohistochemical analysis of the distribution of the **ED-B**-containing **FN isoform** (B-**FN**) in human tissues. The results show that while in normal, adult, human tissues total **FN** has a widespread distribution, the B-**FN isoform** is restricted only to synovial cells, to some vessels and areas of the interstitium of the ovary, and to the myometrium. On the contrary, the B-**FN isoform** has a much greater expression in **fetal** and tumor tissues. These results demonstrate that, in vivo, different **FN isoforms** have a differential distribution and indicate that the B-**FN isoform** may play a role in ontogenesis and oncogenetic processes.

FILE 'HOME' ENTERED AT 14:37:09 ON 29 JUN 2001

and alpha 1-6 and alpha v and beta 1-4 integrin subunits on cryosections of normal human breast, the spectrum of fibrocystic disease (FCD), and benign and malignant breast neoplasms. **Fetal** breast ducts were surrounded by broad Ten bands; adult breast ducts and acini were encompassed by thin continuous rims. In FCD, Ten was detectable and was clearly enhanced around hyperplastic ducts. Fibroadenomas showed uneven Ten periductal reactions while in all carcinomas, the stroma showed extensive and strong reactions that were most intense at the tumors' invasive edge. EDA-cFn's distribution was similar to Ten's but the staining was stronger while **EDB**- and Onc-cFn were virtually restricted to **fetal** breasts and carcinomas. In the normal adult breast, alpha 1,2,3 and alpha 6, and B1 and beta 4 integrins were detected in myoepithelial cells; weaker staining was also noted in the basolateral aspect of luminal cells; this profile was retained--and at times enhanced--in FCD, fibroadenomas and in situ carcinomas in which myoepithelial elements were present. In carcinomas, particularly in those of high grade, integrins tended to be reduced. However, mucinous carcinomas showed enhanced expression and the emergence of alpha 5 integrin that was not in the normal repertory; also a subset of infiltrating lobular carcinomas showed prominent alpha 1 and alpha 6 and beta 1 and--rarely--beta 4 staining distributed in delicate cytoplasmic processes (kinetopodia). These data indicate that the complex cell-matrix and cell-cell interactions of the normal breast are slightly altered in hyperplastic processes and benign neoplasms whereas profound chances occur in carcinomas. The latter display enhanced Ten and EDA- and Onc-cFn expression in particular, while most integrins appear decreased. Notably, mucinous and some lobular carcinomas display enhancement of certain integrins. The conspicuous localization of integrins in kinetopodia may be significant in relation to the invasive behavior of lobular carcinomas.

L13 ANSWER 47 OF 52 MEDLINE DUPLICATE 35

ACCESSION NUMBER:	93154526 MEDLINE
DOCUMENT NUMBER:	93154526 PubMed ID: 7679082
TITLE:	Human amnion epithelial cells assemble tenascins and three **fibronectin isoforms** in the extracellular matrix.
AUTHOR:	Linnala A; Balza E; Zardi L; Virtanen I
CORPORATE SOURCE:	Department of Anatomy, University of Helsinki, Finland.
SOURCE:	FEBS LETTERS, (1993 Feb 8) 317 (1-2) 74-8. Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY:	Netherlands Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals

ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930326
Last Updated on STN: 19960129
Entered Medline: 19930305

AB Monoclonal antibodies (MAb) were used to show that cultured human amnion epithelial (HuA) cells produce tenascins (Tn) and **isoforms** of cellular **fibronectin** (cFn). Tn polypeptides of M(r) 280,000 and 190,000, assembled into extracellular matrix (ECM) but not secreted into the culture medium by HuA cells, were electrophoretically similar to those produced by human fibroblasts as revealed with domain-specific MAbs. The results suggested that most **Fn** produced by HuA cells contained the extradomain (ED) A and an **oncofetal** domain but only a minor fraction **EDB**. In immunofluorescence Tn and **Fn** were seen in different cytoplasmic granules upon monensin-induced intracellular accumulation. Tn appeared to be deposited in the ECM in colocalization with **Fn** but distinctly slower. The present results show that cultured normal human epithelial cells synthesize Tn and three **isoforms** of cFn and secrete them by using different cytoplasmic pathways.

L13 ANSWER 48 OF 52 MEDLINE DUPLICATE 36
ACCESSION NUMBER: 92137345 MEDLINE
DOCUMENT NUMBER: 92137345 PubMed ID: 1310473
TITLE: Differential expression of the **fibronectin isoform** containing the **ED-B oncofetal** domain in normal human fibroblast cell lines originating from different tissues.
AUTHOR: Borsi L; Balza E; Allemanni G; Zardi L
CORPORATE SOURCE: Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
SOURCE: EXPERIMENTAL CELL RESEARCH, (1992 Mar) 199 (1) 98-105.
Journal code: EPB; 0373226. ISSN: 0014-4827.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920329
Last Updated on STN: 19920329
Entered Medline: 19920310

AB **Fibronectin** (**FN**) polymorphism is due both to alternative splicing of three sequences (ED-A, **ED-B**, and IIICS) of the primary transcript and to post-translational modifications. The **FN isoform** containing the **ED-B** sequence (B-**FN**), while having an extremely restricted distribution in normal adult

tissues, has a high expression in **fetal** and tumor tissues. On a panel of non-**fetal** skin, **fetal** skin, and **fetal** lung fibroblast cell lines we have studied, through S1-nuclease protection analysis, the expression of the **ED-B** containing **FN** mRNA as well as the expression of the **ED-B** containing **FN isoform** through immunoblotting and immunofluorescence techniques, using domain specific monoclonal antibodies. The results show that the expression of B-**FN** in the different fibroblast cell lines has an extremely great variability depending on the developmental stage of the donor and on the tissue of origin. Moreover, we found that SV-40-transformed fibroblasts present a higher expression of B-**FN** mRNA with respect to their normal counterparts. An increase in the relative amount of the B-**FN** **isoform** in normal human fibroblasts was also obtained by treatment with transforming growth factor-beta.

L13 ANSWER 49 OF 52 MEDLINE DUPLICATE 37
ACCESSION NUMBER: 92326331 MEDLINE
DOCUMENT NUMBER: 92326331 PubMed ID: 1378105
TITLE: Differential distribution of tenascin and cellular **fibronectins** in acute and chronic renal allograft rejection.
AUTHOR: Gould V E; Martinez-Lacabe V; Virtanen I; Sahlin K M; Schwartz M M
CORPORATE SOURCE: Department of Pathology, Rush Medical College, Chicago, Illinois.
SOURCE: LABORATORY INVESTIGATION, (1992 Jul) 67 (1) 71-9. Journal code: KZ4; 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920821
Last Updated on STN: 19960129
Entered Medline: 19920812

AB BACKGROUND: Acute and chronic renal allograft rejection injuries involve, albeit variably, all compartments of the organ and are associated with significant structural changes. We hoped to gain new insights into these phenomena by determining distribution of certain extracellular matrix proteins known to be involved in architectural remodeling processes. EXPERIMENTAL DESIGN: Frozen tissue samples from biopsies of acute (n = 14) and chronic (n = 12) human renal allograft rejections were studied to compare distribution of tenascin, the extradomains A and B (EDA, **EDB**), and **oncofetal** (Onc) **isoforms** of cellular **fibronectin** (cFn). Normal kidneys (n = 4) served as

controls. Cryosections were immunostained by the avidin-biotin-complex method with monoclonal antibodies specific for those molecules. RESULTS: In acute rejection, reactivity for tenascin and EDA-cFn was increased slightly to moderately in glomerular mesangia and in most vessels while it was intensely and diffusely increased in the interstitium. Rarely were focal **EDB**-cFn and Onc-cFn reactions seen in lesions deemed to reflect acute injury. In chronic rejection, tenascin and EDA-cFn were strongly increased in most glomerular mesangia and in vascular walls but unevenly in the interstitium. In rare glomerular synechiae and vessels, enhanced staining for tenascin and EDA-cFn as well as **EDB**-cFn and Onc-cFn was noted while in obsolete glomeruli only **EDB**-cFn and Onc-cFn were detected. The enhanced distribution of tenascin and EDA-cFn partly reflected that noted during nephrogenesis, whereas staining patterns for **EDB** -cFn and Onc-cFn differed from their **fetal** counterparts. CONCLUSIONS: Tenascin and EDA-cFn are strongly and preferentially expressed in the interstitial and vascular compartments of acute and chronic renal rejection injury suggesting that, in these sites, active repair and remodeling occur during both phases of the rejection process irrespective of the changes seen by conventional microscopy. Tenascin, EDA-cFn as well as **EDB**-cFn and Onc-cFn are all involved, albeit variably, in the glomerular and vascular alterations of chronic rejection. The finding of tenascin and of the three **isoforms** of cFn in glomerular synechiae with actively proliferating epithelium suggests that certain epithelial cells might partake in the synthesis of these molecules.

L13 ANSWER 50 OF 52 MEDLINE DUPLICATE 38

ACCESSION NUMBER: 91241550 MEDLINE
DOCUMENT NUMBER: 91241550 PubMed ID: 2035837
TITLE: Procedure for the purification of the **fibronectin** proteolytic fragments containing the **ED-B oncofetal** domain.
AUTHOR: Borsi L; Balza E; Leprini A; Ponassi M; Zardi L
CORPORATE SOURCE: Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
SOURCE: ANALYTICAL BIOCHEMISTRY, (1991 Feb 1) 192 (2) 372-9. Journal code: 4NK; 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199106
ENTRY DATE: Entered STN: 19910714
Last Updated on STN: 20000303
Entered Medline: 19910627

AB **Fibronectin** (**FN**) is the blend of structurally different molecules (**isoforms**) whose makeup varies depending on the **FN** sources. **Fibronectin** polymorphism is caused by three sequences (called ED-A, **ED-B**, and IIICS) which may be included or excluded from the **FN** molecule depending on the alternative splicing patterns of a single primary transcript. The sequence **ED-B**, which is a complete type III repeat of 91 amino acids, presents some interesting peculiarities: it is the most conserved **FN** region and, in normal adult tissues, the **ED-B**-containing **FN** has an extremely restricted distribution while having a much greater expression in **fetal** and tumor tissues (Carnemolla et al., 1989, J. Cell Biol. 108, 1139-1148), suggesting that the **ED-B** sequence may confer to the **FN** molecules specific biological activities required during ontogenesis and oncogenetic processes. Here we describe a detailed procedure to purify **fibronectin** fragments containing the **ED-B** sequence. These purified fragments are useful reagents in the study of the biological function(s) of the **ED-B**-containing **FN** molecules.

L13 ANSWER 51 OF 52 MEDLINE DUPLICATE 39
ACCESSION NUMBER: 91283948 MEDLINE
DOCUMENT NUMBER: 91283948 PubMed ID: 1711919
TITLE: Expression of tenascin and of the **ED-B** containing **oncofetal fibronectin isoform** in human cancer.
AUTHOR: Nicolo G; Salvi S; Oliveri G; Borsi L; Castellani P; Zardi L
CORPORATE SOURCE: Laboratory of Anatomic Pathology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
SOURCE: CELL DIFFERENTIATION AND DEVELOPMENT, (1990 Dec 2) 32 (3) 401-8. Ref: 28
Journal code: CDD; 8811335. ISSN: 0922-3371.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910825
Last Updated on STN: 19960129
Entered Medline: 19910806
AB Tenascin (TN) and the **oncofetal ED-B** containing **fibronectin isoform** (B-**FN**)

have been reported to be stromal markers of a number of malignancies. Here we report on studies of the distribution of TN and B-**FN** in normal adult tissues and in benign and malignant tumors, as well as on the levels of the B-**FN** mRNA in cultured **fetal** and non-**fetal** human fibroblasts originating from different tissues. B-**FN** has an extremely restricted distribution in normal adult tissues, is not expressed in benign tumors, but is greatly expressed in a high percentage of malignant tumors. On the contrary, human TN in normal adult tissues is less restricted than what has previously been reported and it is largely expressed in a number of both benign and malignant tumors. Moreover, we observed a great variability in the relative amount of B-**FN** mRNA among the 17 normal human fibroblast cell lines tested. We found very low levels in non-**fetal** skin fibroblasts and higher levels in **fetal** lung fibroblasts. We also found differences in the relative amounts of B-**FN** mRNA between fibroblast cell lines originating from the skin and the lung of the same subject.

L13 ANSWER 52 OF 52 MEDLINE DUPLICATE 40
ACCESSION NUMBER: 89155561 MEDLINE
DOCUMENT NUMBER: 89155561 PubMed ID: 2646306
TITLE: A tumor-associated **fibronectin** **isoform** generated by alternative splicing of messenger RNA precursors.
AUTHOR: Carnemolla B; Balza E; Siri A; Zardi L; Nicotra M R; Bigotti A; Natali P G
CORPORATE SOURCE: Cell Biology Laboratory, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.
SOURCE: JOURNAL OF CELL BIOLOGY, (1989 Mar) 108 (3) 1139-48. Journal code: HMV; 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198904
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306
Entered Medline: 19890420

AB **Fibronectin** (**FN**) represents the mixture of a number of structurally different molecules (**isoforms**) whose make-up varies depending on the **FN** sources. **FN** from cultured transformed human cells has a very different **isoform** composition with respect to its normal counterpart. In fact, SV-40-transformed WI-38VAI3 human fibroblasts produce high levels of a **FN** **isoform** (B-**FN**) which is very poorly expressed in their normal, WI-38, counterpart. We have recently demonstrated that the B-**FN**

L13 ANSWER 16 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:123625 SCISEARCH
THE GENUINE ARTICLE: YU933
TITLE: Isolation and characterization of human tumor-derived capillary endothelial cells: Role of **oncofetal fibronectin**
AUTHOR: Alessandri G (Reprint); Chirivi R G S; Castellani P; Nicolo G; Giavazzi R; Zardi L
CORPORATE SOURCE: IST NAZL RIC CANC, CELL BIOL LAB, LARGO ROSANNA BENZI 10, I-16132 GENOA, ITALY (Reprint); IST NAZL RIC CANC, PATHOL LAB, I-16132 GENOA, ITALY; MARIO NEGRI INST PHARMACOL RES, LAB BIOL & THERAPY METASTASIS, I-24100 BERGAMO, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: LABORATORY INVESTIGATION, (JAN 1998) Vol. 78, No. 1, pp. 127-128.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 0023-6837.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 18

L13 ANSWER 17 OF 52 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1998068534 MEDLINE
DOCUMENT NUMBER: 98068534 PubMed ID: 9406699
TITLE: A pilot pharmacokinetic and immunoscintigraphic study with the technetium-99m-labeled monoclonal antibody BC-1 directed against **oncofetal fibronectin** in patients with brain tumors.
AUTHOR: Mariani G; Lasku A; Pau A; Villa G; Motta C; Calcagno G; Taddei G Z; Castellani P; Syrigos K; Dorcaratto A; Epenetos A A; Zardi L; Viale G A
CORPORATE SOURCE: Nuclear Medicine Service, DIMI, University of Genoa, Italy.
SOURCE: CANCER, (1997 Dec 15) 80 (12 Suppl) 2484-9.
Journal code: CLZ; 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19980102
AB BACKGROUND: Preliminary experiments in an animal model have shown

the favorable tumor targeting potential in vivo of radiolabeled BC-1, an immunoglobulin (Ig)G1 monoclonal antibody (MoAb) that recognizes the human **fibronectin isoform** (B+) containing the **ED-B oncofetal** domain. This antigen has extremely restricted distribution in normal adult tissues. Instead, it is highly expressed in **fetal** and tumor tissues, especially in high grade astrocytomas and malignant gliomas of the brain, in which the process of neoangiogenesis linked to tumor growth is particularly important. METHODS: This study was carried out with five patients who had malignant brain tumors (four gliomas and one malignant angioblastic meningioma). The BC-1 MoAb was labeled with technetium-99m (99mTc) by MDP transchelation. Planar and single photon emission computed tomography (SPECT) imaging was acquired at 4-6 and 20 hours after intravenous injection of about 450 MBq/0.2 mg 99mTc-BC-1 and was compared with the nonspecific indicator of blood-brain barrier disruption, 99mTc-diethylenetriamine pentaacetic acid (DTPA). Plasma pharmacokinetic analysis was based on serial blood sampling. All patients underwent potentially curative surgery at the end of the study. RESULTS: The plasma clearance curves were biexponential, with average T(1/2) values of 2-4 hours and 28-33 hours, respectively. 99mTc-BC-1 showed very low nonspecific uptake in the bone marrow, liver, and spleen. Planar and SPECT imaging with 99mTc-BC-1 visualized brain tumors in all patients, with a pattern of intratumor distribution that specifically identified areas of peripheral tumor growth more accurately than the nonspecific indicator, 99mTc-DTPA. Tumor uptake of 99mTc-BC-1 was correlated with the expression of the specific **oncofetal fibronectin**, as shown by immunohistochemistry on surgical samples. CONCLUSIONS: These results indicate the diagnostic potential of MoAb 99mTc-BC-1 for immunoscintigraphy in cancer patients, at least when neoangiogenesis induced by cancer is particularly important.

L13 ANSWER 18 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:19709 SCISEARCH
THE GENUINE ARTICLE: YM158
TITLE: Tumor targeting potential of the monoclonal antibody BC-1 against **oncofetal fibronectin** in nude mice bearing human tumor implants
AUTHOR: Mariani G (Reprint); Lasku A; Balza E; Gaggero B; Motta C; DiLuca L; Dorcaratto A; Viale G A; Neri D; Zardi L
CORPORATE SOURCE: UNIV GENOA, DIMI, NUCL MED SERV, VIALE BENEDETTO XV 6, I-16132 GENOA, ITALY (Reprint); IST NAZL RIC CANC, CELL BIOL LAB, I-16132 GENOA, ITALY; CNR, INST CLIN PHYSIOL, I-56100 PISA, ITALY; UNIV GENOA, INST NEUROSURG, I-16132 GENOA, ITALY; SWISS FED INST

TECHNOL, INST MOL BIOL & BIOPHYS, ZURICH, SWITZERLAND
COUNTRY OF AUTHOR: ITALY; SWITZERLAND
SOURCE: CANCER, (15 DEC 1997) Vol. 80, No. 12, Supp. [S], pp. 2378-2384.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0008-543X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 16
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB BACKGROUND. The immunoglobulin G(1) (IgG(1)) monoclonal antibody (MoAb) BC-1 detects human **oncofetal fibronectin**, which has extremely restricted distribution in normal adult tissues and is highly expressed in **fetal** and tumor tissues.

METHODS. We studied the biodistribution of I-125-labeled MoAb BC-1 in nude mice bearing subcutaneous human tumor implants of U87MG high-grade astrocytoma and SKMel28 melanoma. I-125-BC-1 was injected either intraperitoneally (i.p.) or intravenously (i.v.), and biodistribution was measured up to 144 hours after injection. In animals bearing SKMel28 implants, tumor targeting was also evaluated by in vivo imaging of the whole mouse by using a dedicated device based on transmitted light excitation after i.v. injection of MoAb BC-1 conjugated with the infrared fluorophore, CY7-bis(N-hydroxy-succinimido)-ester.

RESULTS. I-125-BC-1 showed favorable uptake in the human tumor implants, reaching a maximum of 5.27 +/- 0.48% ID/g in the U87MG astrocytoma (72 hours after i.p. injection). The highest uptake in the SKMel28 melanoma implants was 3.49 +/- 0.25% ID/g (24 hours alter i.v. injection). Microautoradiography of tumor specimens obtained after administration of I-125-BC-1 clearly showed radioactivity uptake within the two tumors replicating the same pattern of distribution as that of the **oncofetal fibronectin** shown by immunohistochemistry with MoAb BC-1. Nonspecific uptake of I-125-BC-1 in the bone marrow and skeletal muscle was much lower than in the tumors. In vivo imaging with the fluorophore-labeled MoAb clearly visualized the tumor implants 72-120 hours after i.v. injection.

CONCLUSIONS. The experimental results obtained in this study demonstrate the favorable tumor targeting potential in vivo of the radiolabeled MoAb BC-1, a useful marker of neo angiogenesis induced by cancer. (C) 1997 American Cancer Society.

L13 ANSWER 19 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 97:404981 SCISEARCH
THE GENUINE ARTICLE: WZ649

TITLE: Differentiation, dedifferentiation, and apoptosis of smooth muscle cells during the development of the human ductus arteriosus

AUTHOR: Slomp J; GittenbergerdeGroot A C (Reprint); Glukhova M A; vanMunsteren J C; Kockx M M; Schwartz S M; Koteliansky V E

CORPORATE SOURCE: LEIDEN UNIV, DEPT ANAT & EMBRYOL, POB 9602, NL-2300 RC LEIDEN, NETHERLANDS (Reprint); LEIDEN UNIV, DEPT ANAT & EMBRYOL, NL-2300 RC LEIDEN, NETHERLANDS; CNRS, URA 1337, PHYSIOPATHOL DEV LAB, PARIS, FRANCE; ECOLE NORMALE SUPER, F-75231 PARIS, FRANCE; GEN HOSP MIDDELHEIM, DEPT PATHOL, ANTWERP, BELGIUM; UNIV WASHINGTON, DEPT PATHOL, SEATTLE, WA 98195

COUNTRY OF AUTHOR: NETHERLANDS; FRANCE; BELGIUM; USA

SOURCE: ARTERIOSCLEROSIS THROMBOSIS AND VASCULAR BIOLOGY, (MAY 1997) Vol. 17, No. 5, pp. 1003-1009.
Publisher: AMER HEART ASSOC, 7272 GREENVILLE AVENUE, DALLAS, TX 75231-4596.
ISSN: 1079-5642.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Differentiation of vascular smooth muscle cells (SMCs) is characterized by several molecular transitions. As differentiation proceeds, proteins of the cytoskeletal and contractile apparatus, such as alpha-smooth muscle actin, smooth muscle myosin, calponin, and heavy caldesmon, and the expression of the membrane-related protein smooth muscle phosphoglucomutase-related protein increase, whereas the expression of other proteins, such as **fibronectin** splice variants with extradomains A (EDA) and B (**EDB**), decreases. In this study, we investigated the differentiation of the SMCs of the ductus arteriosus during the development of intimal thickening. Ascending and descending aortas of the same age were used for comparison because these vessels lack intimal thickening. In the **fetal** ductus arteriosus, a relatively early differentiation of the contractile apparatus was observed compared with the ascending and descending aortas. EDA and **EDB** expression was already low, being similar in the ductus and descending aorta and even lower in the ascending aorta. In the neonatal ductus, SMCs of the media and outer intima were well differentiated and comparable with SMCs of the ascending aorta. Dedifferentiated SMCs, with a low expression of cytoskeletal and contractile proteins and a high expression of EDA and **EDB**, were found in regions in the inner intima that show features of progression of intimal thickening and in areas of cytolytic necrosis in the media. With a technique using in situ end labeling of DNA

fragments, we found extensive apoptosis in the area of cytolytic necrosis and to a lesser extent in these areas of the inner intima. In conclusion, SMCs of the **fetal** ductus arteriosus have an advanced differentiation of the contractile apparatus compared with the adjacent aorta. Reexpression of **fetal** characteristics is seen in a number of cells in inner intima and media of the neonatal ductus arteriosus. The finding of apoptosis in these areas suggests that dedifferentiation and apoptosis are associated processes that may play a role in vascular remodeling.

L13 ANSWER 20 OF 52 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97265298 MEDLINE
DOCUMENT NUMBER: 97265298 PubMed ID: 9111235
TITLE: The distribution of laminins and **fibronectins** is modulated during extravillous trophoblastic cell differentiation and decidual cell response to invasion in the human placenta.
AUTHOR: Korhonen M; Virtanen I
CORPORATE SOURCE: Department of Anatomy, Institute of Biomedicine, University of Helsinki, Finland.
SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (1997 Apr) 45 (4) 569-81.
Journal code: IDZ; 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970508

AB We studied the distribution of laminin (Ln) alpha1-alpha3, beta1-beta3, and gamma1 chains, and of the extradomain-A (EDA) and **EDB** and the **oncofetal** epitope of **fibronectin** (Onc-**Fn**) in extravillous trophoblastic cells and decidua in the human placenta by immunohistochemistry. We found that the transition from villous to extravillous trophoblast was accompanied by emergence of immunoreactivity for EDA-, **EDB**-, and Onc-**Fn** among the cells. Furthermore, whereas the villous trophoblastic basement membrane (BM) contains Ln alpha1, alpha2, beta1, beta2, and gamma1 chains, immunoreactivity for Ln alpha1, beta1, and gamma1, but not for Ln alpha2 and beta2 chains, was detected in association with extravillous trophoblastic cells. Interestingly, although immunoreactivity for the Ln alpha1, alpha2, beta1, beta2, and gamma1 chains was detected in all decidual cell BMs, **EDB-Fn** and Onc-**Fn** were detected only in decidua that had been invaded by the trophoblast. In summary, our results describe distinct changes in the

distribution of Ln and **Fn isoforms** during the differentiation of villous trophoblast into extravillous trophoblastic cells. Furthermore, **EDB**- and Onc-**Fn** are preferentially found in decidua that has been invaded by the trophoblast, indicating that the deposition of these **Fn isoforms** reflects a decidual cell response to invasion.

L13 ANSWER 21 OF 52 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 97393716 MEDLINE
DOCUMENT NUMBER: 97393716 PubMed ID: 9250153
TITLE: Loss of **EDB+ fibronectin isoform** is associated with differentiation of alveolar epithelial cells in human **fetal** lung.
AUTHOR: Arai H; Hirano H; Mushiake S; Nakayama M; Takada G; Sekiguchi K
CORPORATE SOURCE: Department of Pathobiology, Osaka Medical Center, Japan.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1997 Aug) 151 (2) 403-12.
Journal code: 3RS; 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970908
Last Updated on STN: 19970908
Entered Medline: 19970826

AB Cell-matrix interactions have been shown to regulate the development of the lung, particularly airway branching and alveolarization. **Fibronectin** is the major constituent of pulmonary extracellular matrix and exists in multiple **isoforms** arising from alternative RNA splicing. EDA and **EDB** are the two major alternatively spliced segments, the expression of which is regulated in a spatiotemporal and oncodevelopmental manner. In this study, we investigated immunohistochemically the distribution of the EDA- and **EDB**-containing **fibronectin isoforms** (referred to as EDA+ **fibronectin** and **EDB+ fibronectin**, respectively) in normal and hypoplastic human lungs at different gestational ages to explore the role of these **fibronectin isoforms** in alveolarization. EDA+ **fibronectin** was expressed around the distal airspaces throughout the development of both normal and hypoplastic lungs. In contrast, the expression of **EDB+ fibronectin** was restricted to the lung with morphologically immature acinar complex, typically observed in normally developing lungs of < 30 gestational weeks or in hypoplastic lungs. To further

confirm the restricted expression of **EDB+ fibronectin** in immature acinar complex, we examined the correlation of **EDB+ fibronectin** expression with that of the surfactant protein SP-A, a biochemical marker for the differentiated type II pneumocytes. A clear inverse relationship between the immunoreactivities for **EDB+ fibronectin** and SP-A was observed in both control and hypoplastic lungs. Given the proposed importance of **fibronectins** in the differentiation of alveolar epithelial cells, our results suggest that the **EDB** segment plays a regulatory role in the differentiation of immature acinar epithelial cells into type II pneumocytes. The **EDB** segment may also serve as a new histochemical marker for the functional maturity of **fetal** lung tissues.

L13 ANSWER 22 OF 52 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1997:237953 BIOSIS
DOCUMENT NUMBER: PREV199799537156
TITLE: Loss of **EDB+ fibronectin isoform** is associated with differentiation of alveolar epithelial cells in human **fetal** lung.
AUTHOR(S): Arai, Hirokazu (1); Mushiake, Sotaro; Nakayama, Masahiro; Takada, Goro; Sekiguchi, Kiyotoshi (1)
CORPORATE SOURCE: (1) Dep. Pathobiol., Osaka Med. Center, Research Inst. Maternal Child Health, Osaka Japan
SOURCE: Pediatric Research, (1997) Vol. 41, No. 4 PART 2, pp. 245A.
Meeting Info.: Meeting of the American Pediatric Society and the Society for Pediatric Research Washington, D.C., USA May 2-6, 1997
ISSN: 0031-3998.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L13 ANSWER 23 OF 52 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97288958 MEDLINE
DOCUMENT NUMBER: 97288958 PubMed ID: 9143890
TITLE: The expression of tenascin and **fibronectin** in keratoconus, scarred and normal human cornea.
AUTHOR: Tuori A; Virtanen I; Aine E; Uusitalo H
CORPORATE SOURCE: Department of Anatomy, University of Helsinki, Finland.
SOURCE: GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, (1997 Apr) 235 (4) 222-9.
Journal code: FPR; 8205248. ISSN: 0721-832X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19970812
Entered Medline: 19970728

AB BACKGROUND: The etiology and pathogenesis of keratoconus remain unclear, and therefore we decided to study the distribution of different **isoforms** of tenascin (Tn) and **fibronectin** (**Fn**) in normal human corneas and in those obtained from penetrating keratoplasty for keratoconus and corneal scarring. METHODS: Frozen sections of human cornea and conjunctiva were stained by immunohistochemical methods with a panel of monoclonal antibodies (MAbs) against different **isoforms** of Tn and **Fn**. RESULTS: In the normal human eye, Tn was found in the limbal and conjunctival basement membrane region, in the conjunctival blood vessels and at the junction of the cornea and sclera, but no immunoreaction was seen in the normal cornea. In the corneas from the keratoconus patients, a clear immunoreaction for Tn was seen in the defects of Bowman's membrane as well as in the distorted stroma beneath the defects. In some of the keratoconus corneas, basement membrane adjacent to the defects also showed reactivity for Tn, and in clinically and histologically scarred keratoconus corneas the scars expressed Tn. In the scarred corneas, only blood vessels in the posterior portion of the cornea showed immunoreactivity for Tn, while no Tn was noted in the scar area or in Bowman's membrane. No major differences were noticed in the reactivity of different MAbs against Tn **isoforms**. **Fn**, extradomain A **Fn** (EDA-**Fn**) and **oncofetal Fn** (onc-**Fn**) were found in the basement membrane of the central cornea of the normal eye. In keratoconus corneas, the defects and clinical and histological scars bound MAbs against **Fn**, EDA-**Fn** and onc-**Fn** , but in the scarred corneas no enhancement in the expression of **Fns** was noted. Extradomain B cellular **Fn** (**EDB-Fn**) was not expressed in any of the eyes studied. CONCLUSIONS: The results suggest that the anterior portion of the cornea is involved in the pathogenesis of keratoconus. Furthermore, it seems that the expression of Tn and **Fns** in the clinically scarred keratoconus corneas is due to a process in which both repairing and scar-forming mechanisms operate at the same time. However, the origin of the defects in Bowman's membrane seen in keratoconus still remains unclear. They may be minor scars due to the disease or primary defects in the process leading to keratoconus.

L13 ANSWER 24 OF 52 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 97060449 MEDLINE

DOCUMENT NUMBER: 97060449 PubMed ID: 8903484
TITLE: Phage antibodies with pan-species recognition of the **oncofoetal** angiogenesis marker **fibronectin ED-B** domain.
AUTHOR: Carnemolla B; Neri D; Castellani P; Leprini A; Neri G; Pini A; Winter G; Zardi L
CORPORATE SOURCE: Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1996 Nov 4) 68 (3) 397-405.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961223

AB **Fibronectin** (**FN**) exists in several polymorphic forms due to alternative splicing. The B-**FN** **isoform** (with **ED-B** domain inserted by splicing) is present in the stroma of **foetal** and neoplastic tissues and in adult and neoplastic blood vessels during angiogenesis but is undetectable in mature vessels. This **isoform**, therefore, represents a promising marker for angiogenesis, as already shown using the mouse monoclonal antibody (MAb) BC-1 directed against an epitope on human B-**FN**. However, this MAb does not directly recognise the human **ED** **-B** domain nor does it recognise B-**FN** of other species; therefore, it cannot be used as a marker of angiogenesis in animal models. In principle, antibodies directed against the human **ED-B** domain should provide pan-species markers for angiogenesis as the sequence of this domain is highly conserved in different species (and identical in humans and mice). As it has proved difficult to obtain such antibodies by hybridoma technology, we used phage display technology. Here, we describe the isolation of human antibody fragments against the human **ED-B** domain that bind to human, mouse and chicken B-**FN**. As shown by immunohistochemistry, the antibody fragments stain human neoplastic tissues and the human, mouse and chicken neovasculature.

L13 ANSWER 25 OF 52 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 96255927 MEDLINE
DOCUMENT NUMBER: 96255927 PubMed ID: 8705761
TITLE: Matrix remodelling in dilated cardiomyopathy entails the occurrence of **oncofetal** **fibronectin** molecular variants.

AUTHOR: Gabler U; Berndt A; Kosmehl H; Mandel U; Zardi L; Muller S; Stelzner A; Katenkamp D
CORPORATE SOURCE: Institute of Pathology, University of Jena, Germany.
SOURCE: HEART, (1996 Apr) 75 (4) 358-62.
Journal code: CEN; 9602087. ISSN: 1355-6037.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19960919
Entered Medline: 19960912

AB OBJECTIVES: To investigate whether disturbance of the cellular homoeostasis and integrity of cardiomyocytes in dilated cardiomyopathy (DCM) is accompanied by alterations in cell-matrix relations as indicated by changes in the deposition of **fibronectin (FN) isoforms**. DESIGN: Tissue from a case series of patients with DCM was investigated by immunohistochemistry with antibodies against **FN** (all variants, clone IST4), ED-A+ **FN** (clone IST9), **ED-B+ FN** (clone BC1), and **oncofetal** glycosylated **FN** (clone 5C10). The sites of de novo synthesis of **FN** were demonstrated by means of non-radioactive RNA in situ hybridisation (ISH) with biotinylated **FN** cDNA fragments as the probe. SETTING: University hospital. PATIENTS: Samples from 10 patients with clinical criteria and histological diagnosis of DCM and from 3 individuals with normal hearts. INTERVENTIONS: Samples were obtained by right ventricular endomyocardial biopsy. MAIN OUTCOME MEASURE: Distribution of **oncofetal FN** variants in DCM hearts. RESULTS: Immunostaining of **FN** (IST4, all variants) showed a coarse interstitial network in normal and diseased myocardium. ED-A+ **FN** was deposited as fine interstitial spots in normal myocardium and in DCM samples. Immunostaining for **oncofetal** glycosylated **FN** and **ED-B+ FN** was not seen in normal adult myocardium, whereas myocardium from DCM patients showed focal and delicate staining in the interstitium. RNA ISH showed that these deposits resulted from local **FN** synthesis. CONCLUSION: The results accord with de novo expression of **oncofetal FN** variants in hearts from patients with DCM. The **oncofetal FN** variants may serve as disease markers in myocardium affected by DCM.

L13 ANSWER 26 OF 52 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97136998 MEDLINE
DOCUMENT NUMBER: 97136998 PubMed ID: 8982375
TITLE: Molecular variants of **fibronectin** and

laminin: structure, physiological occurrence and histopathological aspects.

AUTHOR: Kosmehl H; Berndt A; Katenkamp D
CORPORATE SOURCE: Institute of Pathology, Friedrich Schiller University, Jena, Germany.

SOURCE: VIRCHOWS ARCHIV, (1996 Dec) 429 (6) 311-22. Ref: 132
Journal code: BZD; 9423843. ISSN: 0945-6317.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970127

AB This review deals with biological and pathological aspects of various **isoforms** of the matrix molecules **fibronectin** and laminin. They are generated by different molecular mechanisms: ED-A+ and **ED-B+** **fibronectin** by alternative splicing of pre mRNA, de novo-glycosylated **fibronectin** by alternative post-translational O-linked glycosylation of the IIICS region, and the laminin **isoforms** by exchange of single chains of the heterotrimeric molecule. In contrast to the "common" **fibronectin**, the distribution of **ED-B+** and de novo-glycosylated **fibronectin** is restricted to embryonic tissues; they subsequently reappear in granulation tissue, in fibrosing processes and in tumour stroma. The expression of these so-called **oncofetal fibronectins** is stimulated by growth factors (TGF beta). The association of the **ED-B+ fibronectin** with proliferative activity and newly formed vessels identifies this **fibronectin** variant as a marker of cellular activity in the process of fibrosis and as a suitable agent for the evaluation of tumour angioneogenesis. Initial results suggest a correlation between the amount of **ED-B+** and de novo-glycosylated **fibronectin** in tumour stroma and the behaviour of carcinomas with regard to their invasiveness and propensity for metastatic dissemination. The current nomenclature of the laminin molecule family is presented. The laminin chain constitution of basement membranes switches from embryonic or proliferatively active to adult terminally differentiated tissues [disappearance of the laminin beta 2 (s) chain] and depends on the tissue type. The discrepancy between the loss of basement membranes (multiple basement membrane defects) in carcinomas and the recently reported increased laminin chain synthesis in these tumours may be explained by abundant laminin

chain deposition outside the basement membrane in the carcinoma invasion front, possibly associated with enhanced adhesion of budding tumour cells.

L13 ANSWER 27 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 97:185220 SCISEARCH
THE GENUINE ARTICLE: WK220
TITLE: Characterization of mouse **fibronectin** alternative mRNAs reveals an unusual **isoform** present transiently during liver development
AUTHOR: Gorski G K; Aros M C; Norton P A (Reprint)
CORPORATE SOURCE: THOMAS JEFFERSON UNIV, JEFFERSON MED COLL, DEPT MED, 1020 LOCUST ST, ROOM 365, PHILADELPHIA, PA 19107 (Reprint); THOMAS JEFFERSON UNIV, JEFFERSON MED COLL, DEPT MED, PHILADELPHIA, PA 19107
COUNTRY OF AUTHOR: USA
SOURCE: GENE EXPRESSION, (FEB 1996) Vol. 6, No. 3, pp. 139-149.
Publisher: COGNIZANT COMMUNICATION CORP, 3 HARTSDALE ROAD, ELMSFORD, NY 10523-3701.
ISSN: 1052-2166.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 56

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Fibronectins** are found in many extracellular matrices as well as being abundant plasma proteins. The plasma **isoforms** of **fibronectin**, which are synthesized in the adult by liver hepatocytes, differ from those derived from most other cells and tissues due to alternative mRNA splicing. Studies in several vertebrates have indicated that **FN** alternative splicing is regulated spatially and temporally during development. The mouse represents an attractive organism in which to study the regulation of **fibronectin** splicing during development, but the patterns of **fibronectin** alternative splicing were not known for this species. Mouse **fibronectin** cDNA clones were isolated and sequenced, revealing > 95% identity with rat **fibronectin** at the amino acid level; all three segments that undergo alternative splicing are well conserved. RNase protection and RT-PCR were used to determine the patterns of alternative splicing that occur in fibroblasts and adult liver, sources of cellular and plasma **fibronectins**. Only A - B - mRNAs were detected in liver, and three V region variants were observed, corresponding to the protein **isoforms** V120, V95, and V0. Fibroblasts produced mRNAs that were heterogeneous for A and B splicing, but all RNAs contained V120. These patterns contrast with the embryonic form (B + A + V120). Characterization of **fibronectin** mRNAs from livers of **fetal** and newborn

mice revealed that a significant level of B + mRNA was present throughout late gestation, declining at birth. Little A + mRNA was present, and the adult liver V region pattern was observed at all stages. Thus, **fibronectin** splicing changes during liver development are noncoordinate. One consequence of this temporal regulation is the transient synthesis of B + mRNAs, including a novel **isoform**, B + A - V0.

L13 ANSWER 28 OF 52 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96419339 MEDLINE
DOCUMENT NUMBER: 96419339 PubMed ID: 8822112
TITLE: Differential expression of **fibronectin** splice variants, **oncofetal** glycosylated **fibronectin** and laminin **isoforms** in nodular palmar fibromatosis.
AUTHOR: Kosmehl H; Berndt A; Katenkamp D; Mandel U; Bohle R; Gabler U; Celeda D
CORPORATE SOURCE: Institute of Pathology, University of Jena, Germany.
SOURCE: PATHOLOGY, RESEARCH AND PRACTICE, (1995 Nov) 191 (11) 1105-13.
Journal code: PBZ; 7806109. ISSN: 0344-0338.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961114

AB The tissue formation process in nodular palmar fibromatosis (Morbus Dupuytren) was investigated by the demonstration of **fibronectin** splice variants (ED-A and **ED-B fibronectin**), de novo glycosylated **fibronectin** and laminin **isoforms** (A, M, B1, B2, s chains) in association to the proliferative activity (Ki-67 antigen) and the occurrence of myofibroblast phenotype (alpha-smooth muscle actin, desmin). The proliferative noduli of the fibromatosis were characterized by a diffuse immunostaining for alpha-smooth muscle actin, and single cells positive for desmin and the Ki-67 antigen. In contrast to the surrounding aponeurosis as extracellular matrix, components of the whole proliferative noduli were defined: ED-A, **ED-B** and de novo glycosylated **fibronectin**, B1 and B2 laminin chain, tenascin and collagen type IV. The demonstration of the A and M laminin chain was restricted to a few cells of the proliferative noduli. S laminin could be visualized in the majority of palmar aponeurotic fibroblasts. As revealed by mRNA, in situ hybridization a de novo synthesis of **fibronectin** could only be detected within proliferative noduli. There is a positive

correlation between the myofibroblast phenotype formation, cellular proliferation and the occurrence of ED-A and **ED-B** containing **fibronectin**, as well as de novo glycosylated **fibronectin** in Dupuytren's disease. The ultrastructural irregularities of myofibroblastic basal lamina and the heterogeneity of the myofibroblast phenotype are equivalent to the variability of laminin **isoform** immunostaining.

L13 ANSWER 29 OF 52 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96381390 MEDLINE
DOCUMENT NUMBER: 96381390 PubMed ID: 8789403
TITLE: TGF beta and bFGF synthesis and localization in Dupuytren's disease (nodular palmar fibromatosis) relative to cellular activity, myofibroblast phenotype and **oncofetal** variants of **fibronectin**.
AUTHOR: Berndt A; Kosmehl H; Mandel U; Gabler U; Luo X; Celeda D; Zardi L; Katenkamp D
CORPORATE SOURCE: Institute of Pathology, Friedrich Schiller University, Jena, Germany.
SOURCE: HISTOCHEMICAL JOURNAL, (1995 Dec) 27 (12) 1014-20. Journal code: G9A; 0163161. ISSN: 0018-2214.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961106
Last Updated on STN: 19961106
Entered Medline: 19961024

AB Nodular palmar fibromatosis is a self-limited proliferation of fibro-/myofibroblasts associated with growth factor synthesis and abundant **fibronectin** extracellular matrix deposition. bFGF and TGF beta are potent modulators of fibro-/myofibroblast proliferation and differentiation. Moreover, in vitro investigations evidenced a TGF beta 1-dependent regulation of alternative splicing of **fibronectin** mRNA. To investigate a possible implication of these growth factors in the tissue formation process of palmar fibromatosis, TGF beta 1/2 and bFGF synthesis, as well as TGF beta 1/3 and bFGF tissue distribution, is demonstrated by RNA in situ hybridization and/or immunohistochemistry in relation to myofibroblast phenotype development (alpha-smooth muscle actin, desmin immunohistochemistry), expression of different **fibronectin isoforms** (ED-A+, **ED-B+** and **oncofetal** glycosylated **fibronectin** immunohistochemistry, **fibronectin** RNA in situ hybridization) and cellular activity (cyclin RNA in situ hybridization, Ki-67 immunolabelling). The myofibroblast phenotype

(alpha-smooth muscle actin, desmin), the growth factor synthesis (TGF beta 1 and 2, bFGF), **fibronectin** matrix synthesis (RNA in situ hybridization with cDNA) and ED-A+, **ED-B+** and **oncofetal** glycosylated **fibronectin** immunostaining are exclusively localized in the active proliferative nodules (Ki-67 immunolabelling and cyclin mRNA demonstration). Whereas the growth factor synthesis is restricted to the proliferative areas of the fibromatosis only, TGF beta 1, TGF beta 3 and bFGF proteins can also be detected immunohistochemically with a lower intensity in the surrounding aponeurotic tissue. The spatial correlation of myofibroblast phenotype, TGF beta and bFGF synthesis and the occurrence of the **oncofetal** molecular **fibronectin** variants (**ED-B+** and **oncofetal** glycosylated **fibronectin**) in the active proliferative fibromatosis nodules suggests a pathogentic role of these growth factors and matrix components in the tumorous tissue formation process. The presence of the bFGF and TGF beta 1/3 proteins in fibroblasts neighbouring the proliferative nodules may point to a recruitment of quiescent aponeurotic fibroblasts in the fibromatous tissue formation process.

L13 ANSWER 30 OF 52 MEDLINE DUPLICATE 21

ACCESSION NUMBER: 96054924 MEDLINE
DOCUMENT NUMBER: 96054924 PubMed ID: 7576694
TITLE: Transforming growth factor-beta regulates the expression of **fibronectin** and tenascin in BEAS 2B human bronchial epithelial cells.
AUTHOR: Linnala A; Kinnula V; Laitinen L A; Lehto V P; Virtanen I
CORPORATE SOURCE: Department of Anatomy, University of Helsinki, Finland.
SOURCE: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (1995 Nov) 13 (5) 578-85.
Journal code: AOB; 8917225. ISSN: 1044-1549.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19960124
Entered Medline: 19951206

AB We used monoclonal antibodies to study expression and extracellular matrix (ECM) incorporation of tenascin (Tn) and **isoforms** of **fibronectin** (**Fn**) in BEAS 2B immortalized human bronchial epithelial cells and the regulation of their synthesis by transforming growth factor (TGF)-beta 1 and -beta 2. In immunofluorescence microscopy, the control cells appeared negative

for Tn. Extradomain A (EDA)-**Fn** was mainly seen in association with ECM fibers and, in a few cells, in an intracellular location. Immunoreactivity for **oncofetal** (onc)-**Fn** and extradomain B (**EDB**)-**Fn** was only seen in a few cells. In TGF-beta 1- and -beta 2-treated cells, a greatly enhanced immunostaining for Tn and three **isoforms** of **Fn** was seen both as to the number of positive cells and to the amount of immunoreactive material around them. In Western blotting of the untreated cells, EDA-**Fn** and onc-**Fn** were detected in the cell-free ECM and in the culture medium, whereas **EDB**-**Fn** was not detectable. An enhanced secretion and deposition of both EDA-**Fn** and onc-**Fn** and also secretion of **EDB**-**Fn** was seen upon treatment with TGF-beta s. In TGF-beta-treated cells, Tn was found exclusively in the ECM and not in the culture medium as shown by Western blotting of cell-free ECM and culture medium, respectively. Accentuation of tenascin staining in TGF-beta-treated cells was due to a greatly enhanced production of M(r) 280,000 and M(r) 190,000 **isoforms** of Tn.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 31 OF 52 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 95204887 MEDLINE
DOCUMENT NUMBER: 95204887 PubMed ID: 7897185
TITLE: Chondrocyte heterogeneity: immunohistologically defined variation of integrin expression at different sites in human **fetal** knees.
AUTHOR: Salter D M; Godolphin J L; Gourlay M S
CORPORATE SOURCE: Edinburgh University Department of Pathology, UK.
SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (1995 Apr) 43 (4) 447-57.
Journal code: IDZ; 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19950504
Last Updated on STN: 19950504
Entered Medline: 19950426

AB During development and at maturity different forms of cartilage vary in morphology and macromolecular content. This reflects heterogeneity of chondrocyte activity, in part involving differential interactions with the adjacent extracellular matrix via specialized cell surface receptors such as integrins. We undertook an immunohistological study on a series of human **fetal** knee joints to assess variation in the expression of integrins by chondrocytes and potential matrix ligands in articular, epiphyseal, growth plate, and meniscal cartilage. The results show that

articular chondrocytes (beta 1+, beta 5 alpha V+, alpha 1+, alpha 2+/-, alpha 5+, weakly alpha 6+, alpha V+) differed from epiphyseal (beta 1+, beta 5 alpha V+, alpha 1+/-, alpha 2+/-, alpha 5+, alpha 6+, alpha V+) growth plate (beta 1+, beta 5 alpha V+, alpha 1-, alpha 2-, alpha 5+, alpha 6+, alpha V+), and meniscal cells (beta 1+, beta 5 alpha V+, alpha 1+, strongly alpha 2+, alpha 5+, alpha 6+, alpha V+ in expression of integrin subunits. There was no expression of beta 3, beta 4, beta 6, or alpha 3 by chondrocytes. These results differ from previous reports on the expression of integrins by adult articular cartilage, where alpha 2 and alpha 6 are not seen. Variation in distribution of matrix ligands was also seen. **Fibronectin**, laminin and Type VI collagen were expressed in all cartilages but there was restricted expression of tenascin, ED-A and **ED-B fibronectin isoforms** (articular cartilage and meniscus), and vitronectin (absent from growth plate cartilage). Regulated expression of integrins by chondrocytes, associated with changes in the pericellular matrix composition, is of potential importance in control of cartilage differentiation and function in health and disease.

L13 ANSWER 32 OF 52 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 96071025 MEDLINE
DOCUMENT NUMBER: 96071025 PubMed ID: 7591246
TITLE: Tenascin and **fibronectin isoforms** in human renal cell carcinomas, renal cell carcinoma cell lines and xenografts in nude mice.
AUTHOR: Lohi J; Tani T; Laitinen L; Kangas L; Lehto V P; Virtanen I
CORPORATE SOURCE: Department of Anatomy, University of Helsinki, Finland.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1995 Nov 3) 63 (3) 442-9.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951214

AB We studied the expression of tenascin (Tn) and **isoforms** of **fibronectin** (**Fn**) in human renal cell carcinomas (RCC) and oncocytomas, in RCC cell lines and in their s.c. implanted xenografts in nude mice. In well-differentiated RCCs and oncocytomas extra-domain A (EDA)-**Fn** and Tn immunoreactivities were confined to the basement membranes and blood vessels, while in

less-differentiated RCCs they were also widely seen in the stroma, correlating with the morphological differentiation of the tumor. Expression of **EDB-Fn** and **oncofetal** (onc)-**Fn** was very scarce in most of the RCCs and oncocytomas. Western blotting results demonstrated the predominance of the M(r) 190,000 Tn subunit in most RCCs. Among the 4 RCC cell lines, 3 showed Tn in the extracellular matrix. As xenografts, they formed moderately or poorly differentiated tumors, with abundant Tn. Three of the RCC cell lines also showed secretion of EDA-**Fn** and 2 of them secretion of onc-**Fn** and **EDB-Fn** into the culture medium, while in xenografts there was a strong expression of all **Fn isoforms**. In xenografts, the expression of Tn closely recapitulated that seen in clinical tumors and in the cell lines in vitro, while the expression of **Fn isoforms** in cultured cells and their xenografts was highly discordant.

L13 ANSWER 33 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:35422 SCISEARCH
THE GENUINE ARTICLE: TL681
TITLE: SPECIFIC EXPRESSION OF THE **ED-B** CONTAINING **FIBRONECTIN ISOFORM** BY ENDOTHELIAL-CELLS OF GROWING TUMOR VESSELS
AUTHOR: CASTELLANI P; VIALE G; DORCARATTO A; QUERZE G; ALLEMANNI G; ZARDI L; SIRI A (Reprint)
CORPORATE SOURCE: IST NAZL RIC CANC, CELL BIOL LAB, VIALE BENEDETTO XV 10, I-16132 GENOA, ITALY (Reprint); IST NAZL RIC CANC, CELL BIOL LAB, I-16132 GENOA, ITALY; UNIV GENOA, DEPT NEUROSURG, GENOA, ITALY
COUNTRY OF AUTHOR: ITALY
SOURCE: ANTIBODY IMMUNOCONJUGATES AND RADIOPHARMACEUTICALS, (WIN 1995) Vol. 8, No. 4, pp. 325-332. ISSN: 0892-7049.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 21
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The **fibronectin (FN) isoform** containing the **ED-B** sequence (B+**FN**) shows an extremely restricted distribution in normal,adult tissues, while it is highly expressed in **fetal** and tumor tissues: Using the monoclonal antibody (mAb) BC-1, specific for this **FN isoform**, we demonstrate here, using immunohistochemical techniques, that B+**FN** is undetectable in mature vessels and, vice versa, that it is highly expressed during angiogenesis in neoplastic tissues. B+**FN** is thus a marker of new vessel formation in tumors, and the mAb BC-1 may be a

useful reagent to evaluate the level of angiogenetic processes in different neoplasia.

L13 ANSWER 34 OF 52 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95205687 EMBASE
DOCUMENT NUMBER: 1995205687
TITLE: Erratum: The **fibronectin isoform** containing the **ED-B** **oncofetal** domain: A marker of angiogenesis (Int. J. Cancer, 59, 612-618 (1994)).
AUTHOR: Castellani P.; Viale G.; Dorcaratto A.; Nicolo G.; Kaczmarek J.; Querze G.; Zardi L.
SOURCE: International Journal of Cancer, (1995) 62/1 (118). ISSN: 0020-7136 CODEN: IJCNAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 016 Cancer
LANGUAGE: English

L13 ANSWER 35 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 95:468204 SCISEARCH
THE GENUINE ARTICLE: RG069
TITLE: THE **FIBRONECTIN ISOFORM** CONTAINING THE **ED-B** **ONCOFETAL** DOMAIN - A MARKER OF ANGIOGENESIS (VOL 59, PG 612, 1994)
AUTHOR: CASTELLANI P (Reprint); VIALE G; DORCARATTO A; NICOLO G; KACZMAREK J; QUERZE G; ZARDI L
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (04 JUL 1995) Vol. 62, No. 1, pp. 118. ISSN: 0020-7136.
DOCUMENT TYPE: Errata; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 1

L13 ANSWER 36 OF 52 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 95288832 MEDLINE
DOCUMENT NUMBER: 95288832 PubMed ID: 7770960
TITLE: Immunolocalization of cellular **fibronectins** in the normal liver, cirrhosis, and hepatocellular carcinoma.
AUTHOR: Koukoulis G K; Shen J; Virtanen I; Gould V E
CORPORATE SOURCE: Department of Pathology, Rush Medical College, Chicago, IL 60612, USA.
SOURCE: ULTRASTRUCTURAL PATHOLOGY, (1995 Jan-Feb) 19 (1) 37-43. Journal code: WMM; 8002867. ISSN: 0191-3123.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950713
Last Updated on STN: 19950713
Entered Medline: 19950630

AB Cellular (c) **fibronectins** (**Fn**) differ biochemically, immunologically, and functionally from plasma **fibronectins** (pFn). Most existing data on **Fn** distribution in the normal and diseased liver require revision because those studies were based on reagents that did not distinguish pFn from cFn and predated the development of specific cFn monoclonal antibodies (Mabs). We immunostained cryosections of normal adult livers (n = 5), cirrhotic livers (n = 20), and livers with hepatocellular carcinoma (HCC) (n = 10) by the avidin-biotin-complex method with specific Mabs to the extradomains A and B (EDA, **EDB**) and **oncofetal** (Onc) **isoforms** of cFn. Selected samples were stained with an antiserum to pFn; **fetal** livers served as controls. Normal and cirrhotic livers showed EDA-cFn staining in the portal, septal, and perisinusoidal matrix; its distribution was more restricted than that of pFn. In cirrhosis, EDA-cFn reactions were strongest at sites of piecemeal necrosis and around proliferating ductules in biliary cirrhosis. EDA-cFn reactions were consistently most intense in the matrix of HCC. Distinct from adult normal and cirrhotic livers, reactions for **EDB**- and Onc-cFn were noted exclusively in most cases of HCC. We conclude that the only cFn **isoform** indigenous to the normal adult liver matrix is EDA-cFn. Enhanced EDA-cFn in cirrhotic livers may serve as indicator of active stromal remodeling. The restriction of **EDB**- and Onc-cFn to a large subset of HCC and the putative role of cFn in modulating cell-matrix adhesive interactions would suggest that the emergence of these molecules may be related to the variably invasive and metastatic properties of these tumors.

L13 ANSWER 37 OF 52 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 95221026 MEDLINE
DOCUMENT NUMBER: 95221026 PubMed ID: 7705930
TITLE: **Fibronectin isoforms** are differentially expressed in normal and adenomatous human anterior pituitaries.
AUTHOR: Farnoud M R; Farhadian F; Samuel J L; Derome P; Peillon F; Li J Y
CORPORATE SOURCE: Unite INSERM 223, Faculte de Medecine Pitie-Salpetriere, Paris, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1995 Mar 29) 61 (1)

27-34.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19950518
Entered Medline: 19950509

AB The expression of **fibronectin** (**FN**) **isoforms** containing the extradomains A and B (ED-A+ and **ED-B+ FNs**) as well as a differentially O-glycosylated **oncofetal** form of the protein (onf-**FN**) was investigated in 6 normal human anterior pituitaries and 25 human pituitary adenomas. In normal tissue, immunohistochemical experiments showed the presence of **FN** molecules lacking the extradomains A and B (ED-A- and **ED-B- FNs**) without onf-**FN** immunoreactivity. These proteins were localized in the connective tissue compartment and especially in the vessel walls. Analysis of **FN** mRNA demonstrated an in situ synthesis of ED-A- and **ED-B- FNs** in the normal anterior pituitary. By contrast, in the adenomas, immunoreactivity for ED-A+ **FN** was observed in all cases. **ED-B+** and onf-**FN** immunoreactivities were observed in 14 and 8 adenomas, respectively, regardless of the type, grade or invasiveness of the adenomas. ED-A+ **FN** mRNA was expressed in all adenomas studied, and **ED-B+ FN** mRNA was present in **ED-B+** immunoreactive cases only. In pituitary adenomas, these 3 forms of **FN** were specifically associated with the endothelium and vascular smooth-muscle cells. Our results demonstrate that the processes of remodelling of the connective tissue compartment that occur in adenoma angiogenesis are associated with pre- and post-translational alterations of **FN** synthesis leading to the expression of ED-A+, **ED-B + and oncofetal FNs**.

L13 ANSWER 38 OF 52 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 94164738 MEDLINE
DOCUMENT NUMBER: 94164738 PubMed ID: 7509777
TITLE: RT-PCR detection of **fibronectin** EDA+ and **EDB+** mRNA **isoforms**: molecular markers for hepatocellular carcinoma.
AUTHOR: Tavian D; De Petro G; Colombi M; Portolani N; Giulini S M; Gardella R; Barlati S
CORPORATE SOURCE: Department of Biomedical Sciences and Biotechnology, University of Brescia, Italy.

SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1994 Mar 15) 56 (6) 820-5.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-UNKNOWN
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19960129
Entered Medline: 19940407

AB Alternative splicing of **fibronectin** pre-mRNA has been shown to be independently regulated at the EDA and **EDB** regions in a tissue and developmental stage-specific manner. In this study, RT-PCR approaches were developed for the detection of EDA and **EDB FN** mRNA **isoforms** in hepatocarcinoma cells (SK-Hep-I) grown in vitro and in human liver biopsies. While EDA+ and **EDB+ isoforms** were not present in control adult liver, they were detectable in the hepatocarcinoma cells and in **fetal** liver. The RT-PCR analysis, extended to biopsies of malignant and non-malignant hepatic tissues, showed that **FN** mRNAs containing the EDA and **EDB** sequences were present in the 14 hepatocellular carcinomas (HCCs) tested but absent in the non-tumorous liver tissues (i.e., normal parenchyma, non-specific reactive and chronic hepatitis, steatosis). The **EDB+ FN** mRNA **isoforms** were also detected in 3 cases of benign neoplasm (hepatocellular adenoma, HCA, I; nodular focal hyperplasia, NFH, 2), while the EDA+ was only detectable in I of the 2 cases of NFH. In addition, both EDA+ and **EDB+ isoforms** were expressed in 5 out of 9 cirrhotic livers surrounding the tumors. This molecular analysis, which can also be performed on small liver biopsies (2 mg), may therefore be a useful additional tool in the diagnosis of HCC.

L13 ANSWER 39 OF 52 MEDLINE DUPLICATE 27

ACCESSION NUMBER: 95033136 MEDLINE
DOCUMENT NUMBER: 95033136 PubMed ID: 7946273
TITLE: **Oncofetal fibronectins** in oral carcinomas: correlation of two different types.
AUTHOR: Mandel U; Gaggero B; Reibel J; Therkildsen M H; Dabelsteen E; Clausen H
CORPORATE SOURCE: Department of Oral Diagnostics, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, Genoa, Italy.
SOURCE: APMIS, (1994 Sep) 102 (9) 695-702.
Journal code: AMS; 8803400. ISSN: 0903-4641.
PUB. COUNTRY: Denmark

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941222

AB Different **isoforms** of **fibronectin** are derived from a single gene by alternative processing of the primary RNA transcript or by posttranslational modifications. We have previously demonstrated that an **oncofetal fibronectin** (**FN**) **isoform** derived by O-glycosylation is highly associated with malignancy in breast and oral tumors. Another **oncofetal FN isoform** containing the **ED-B** sequence is derived by alternative splicing, and **FN** containing **ED-B** has been found to be a stromal marker of malignancies in various tissues. Here we report a comparative study by immunohistology of the distribution of the **ED-B**-containing **isoform** and the **oncofetal FN isoform** derived by O-glycosylation, in oral squamous cell carcinomas, premalignant lesions, and normal oral mucosa. A selective expression of the **ED-B**-containing **isoform** was demonstrated in close relation to the invading carcinoma (38/38), whereas there was virtually no staining in submucosa underlying premalignant lesions (1/11) and normal epithelium (0/5). The **ED-B**-containing **FN** showed close co-distribution and staining pattern with the **oncofetal isoform** derived by O-glycosylation. These results demonstrate that accumulation of **FN** adjacent to oral carcinomas includes both the **ED-B**-containing **isoform** and the **isoform** derived by O-glycosylation. Although both the change in primary structure and glycosylation of **FN** create conformational and immunologically detectable changes, the functional consequences in association with invasive carcinoma are poorly understood at present. Diagnostic implications especially of borderline lesions as well as evaluation of tumor aggressiveness may, however, be important.

L13 ANSWER 40 OF 52 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 95048898 MEDLINE
DOCUMENT NUMBER: 95048898 PubMed ID: 7525495
TITLE: The **fibronectin isoform** containing the **ED-B** **oncofetal** domain: a marker of angiogenesis.
COMMENT: Erratum in: Int J Cancer 1995 Jul 4;62(1):118
AUTHOR: Castellani P; Viale G; Dorcaratto A; Nicolo G; Kaczmarek J; Querze G; Zardi L

CORPORATE SOURCE: Laboratory of Cell Biology, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1994 Dec 1) 59 (5) 612-8.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19960129
Entered Medline: 19941223

AB Different **fibronectin** (**FN**) **isoforms** are generated by the alternative splicing of 3 regions (ED-A, **ED-B** and IIICS) of the primary transcript. The **FN isoform** containing the **ED-B** sequence, a complete type-III-homology repeat, while having extremely restricted distribution in normal adult tissues, reveals high expression in **fetal** and tumor tissues. Using the monoclonal antibody (MAb) BC-I, specific for the **FN isoform** containing the **ED-B** sequence (B+.**FN**), we demonstrated here, using immunohistochemical techniques, that while this **FN isoform** is undetectable in mature vessels, it is highly expressed during angiogenesis both in neoplastic and in normal tissues, as in the case of the functional layer of endometrium during the proliferative phase. B+.**FN** is thus a marker for the formation of new vessels, and the BC-I MAb may be a useful reagent for evaluating the level of the angiogenetic process in different neoplasms.

L13 ANSWER 41 OF 52 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 94116672 MEDLINE
DOCUMENT NUMBER: 94116672 PubMed ID: 7507066
TITLE: **Isoforms** of cellular **fibronectin** and tenascin in amniotic fluid.
AUTHOR: Linnala A; von Koskull H; Virtanen I
CORPORATE SOURCE: Department of Anatomy, University of Helsinki, Finland.
SOURCE: FEBS LETTERS, (1994 Jan 10) 337 (2) 167-70.
Journal code: EUH; 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940312
Last Updated on STN: 19970203

Entered Medline: 19940218

AB Amniotic fluid (AF) obtained from second trimester pregnancies presented extradomain (ED) A, B and an **oncofetal** (onc-f) domain containing **isoforms** of cellular **fibronectin** (cFn) in Western blotting of gelatin-bound polypeptides and directly of AF. Western blotting after sequential immunoprecipitation suggested at least three **Fn** molecules: one containing EDA and the onc-f domain and another minor component distinctly containing all the domains, and a third one only containing EDA. The immunoblotting results for EDA-cFn and onc-f-cFn were closely similar to that for total **Fn**, whereas in plasma samples of normal and pregnant women only traces of EDA-cFn and onc-f-cFn, but no **EDB**-cFn, were found. Western blotting of AF also indicated the presence of three **isoforms** of tenascin (Tn), M(r) 190,000 and 280,000 polypeptides earlier found in many cells, and a M(r) 200,000 polypeptide, novel for AF and not present in plasma. The results suggest a novel extracellular matrix polypeptide composition for AF.

L13 ANSWER 42 OF 52 MEDLINE DUPLICATE 30

ACCESSION NUMBER: 95066683 MEDLINE
DOCUMENT NUMBER: 95066683 PubMed ID: 7526588
TITLE: Immunohistochemistry of two different types of placental fibrinoid.
AUTHOR: Frank H G; Malekzadeh F; Kertschanska S; Crescimanno C; Castellucci M; Lang I; Desoye G; Kaufmann P
CORPORATE SOURCE: Department of Anatomy, Technical University of Aachen, Germany.
SOURCE: ACTA ANATOMICA, (1994) 150 (1) 55-68.
Journal code: 09A; 0370272. ISSN: 0001-5180.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19960129
Entered Medline: 19941214

AB The structure and composition of human placental fibrinoid were studied on cryostat and paraffin sections and by transmission electron microscopy as well as immunohistochemistry using antibodies directed against fibrin, **fibronectin isoforms**, collagens IV and VI, laminin and tenascin. The findings suggest two structurally and immunohistochemically different subtypes of fibrinoid: fibrin-type fibrinoid and matrix-type fibrinoid. Fibrin-type fibrinoid was characterized by immunoreactivity for fibrin and cellular **fibronectin**, including the ED-A sequence. Immunostaining for all other extracellular matrix

molecules was negative. Ultrastructurally, this fibrinoid subtype consisted of a meshwork of fibers with 20-nm cross striation typical of fibrin. Fibrin-type fibrinoid never contained extravillous trophoblast cells. It is therefore primarily a blood clot product derived from maternal and **fetal** blood. In contrast, matrix-type fibrinoid showed virtually no evidence of fibrin; it was immunopositive for extracellular matrix molecules such as the **fibronectins**, particularly **oncofetal fibronectin** (containing the **ED-B** sequence), collagen IV, laminin and tenascin. **Oncofetal fibronectin**, which was neither expressed in fibrin-type fibrinoid nor in the villous stromal core, seemed to be a specific marker for matrix-type fibrinoid. Single or clustered nonproliferative extravillous trophoblast cells were embedded within the matrix molecules. It is very likely that these cells secrete the matrix in a non-polarized fashion. Fibrin-type fibrinoid would appear to be involved in shaping the intervillous space and in replacing damaged syncytiotrophoblast acting as a transport and immune barrier. Matrix-type fibrinoid, as a secretory product of the extravillous trophoblast, should be discussed in context with the invasive properties of this cell population.

L13 ANSWER 43 OF 52 MEDLINE DUPLICATE 31

ACCESSION NUMBER: 95012838 MEDLINE
DOCUMENT NUMBER: 95012838 PubMed ID: 7927891
TITLE: Distribution of **oncofetal fibronectin isoforms** in normal, hyperplastic and neoplastic human breast tissues.
AUTHOR: Kaczmarek J; Castellani P; Nicolo G; Spina B; Allemanni G; Zardi L
CORPORATE SOURCE: Department of Clinical Pathomorphology, Academy of Medicine, Poznan, Poland.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1994 Oct 1) 59 (1) 11-6.
Journal code: GQU; 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941031

AB Two different **oncofetal fibronectins** (**FN**) have been reported: one, generated by O-glycosylation in the splicing region IIICS that is recognized by monoclonal antibody (MAb) FDC-6, and another, recognized by MAb BC-I, generated by the alternative splicing of the **FN** pre-mRNA which includes an

extra type-III repeat called **ED-B**. Using these and 2 other MAbs (IST-4 which recognizes all different **FN isoforms** and IST-6 which recognizes only the **FN** molecules that do not include the **ED-B** sequence) we have immunohistochemically studied 171 normal, hyperplastic and neoplastic breast-tissue specimens. Although all normal specimens reacted strongly with MAbs IST-4 and IST-6, they did not show the presence of **oncofetal FNs** as established by the use of BC-I and FDC-6. In contrast, out of the 97 cases of invasive ductal carcinomas studied, 90 (93%) and 96 (99%) reacted positively with BC-I and FDC-6, respectively, the reaction being observed in the tumoral stroma connective tissue and in tumoral vessels. Furthermore, invasive lobular carcinoma showed less intense and less frequent staining with BC-1 and FDC-6 (10 and 11 out of 14, respectively). We found differences in the distribution of the 2 **oncofetal fibronectin isoforms** within the same specimens. The most remarkable difference was observed in the tumoral vessels: in invasive ductal carcinoma MAb BC-1 revealed a positive reaction with vessels in 78% of cases while FDC-6 showed such a reaction in only 59% of cases.

L13 ANSWER 44 OF 52 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 93245183 MEDLINE
DOCUMENT NUMBER: 93245183 PubMed ID: 8481903
TITLE: Coordinate oncodevelopmental modulation of alternative splicing of **fibronectin** pre-messenger RNA at ED-A, **ED-B**, and CS1 regions in human liver tumors.
AUTHOR: Oyama F; Hirohashi S; Sakamoto M; Titani K; Sekiguchi K
CORPORATE SOURCE: Institute for Comprehensive Medical Science, Fujita Health University, Aichi, Japan.
SOURCE: CANCER RESEARCH, (1993 May 1) 53 (9) 2005-11. Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19930618
Entered Medline: 19930601

AB The molecular diversity of **fibronectin** arises from alternative RNA splicing at regions termed ED-A, **ED-B**, and IIICS. We investigated the splicing patterns of **fibronectin** pre-mRNA at both **ED-B** and IIICS regions in various human liver tissues with an emphasis on the expression of the alternative cell adhesive site CS1 within the

IIICS region. The relative abundance of the **fibronectin** mRNA containing the CS1 sequence was significantly increased in both **fetal** and cancerous liver tissues, although it was not affected in nonmalignant tissues with chronic hepatitis and cirrhosis. Similarly, the relative abundance of the **fibronectin** mRNA containing the **ED-B** region was also increased in both **fetal** liver and liver tumors, showing a close parallelism with the splicing pattern at the ED-A region. Immunohistochemical examination of cancerous liver tissues with monoclonal antibodies directed to the ED-A and **ED-B** segments revealed that the **fibronectin isoforms** containing these extra peptide segments were specifically deposited in the tumor nodules. Other genes encoding kininogen, gamma chain of fibrinogen, and beta-amyloid protein precursor, all of which had been shown to be alternatively processed, did not show any significant alteration in the splicing pattern in cancerous liver tissues. These results indicate that the alternative splicing of **fibronectin** pre-mRNA at the ED-A, **ED-B**, and IIICS regions is coordinately modulated in both **fetal** and cancerous liver tissues toward inclusion of the extra peptide segments and that not all but only selected genes are susceptible for "fine tuning" of alternative RNA splicing in cancerous liver tissues.

L13 ANSWER 45 OF 52 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 93297090 MEDLINE
DOCUMENT NUMBER: 93297090 PubMed ID: 7685961
TITLE: Immunolocalization of tenascin and cellular **fibronectins** in diverse glomerulopathies.
AUTHOR: Assad L; Schwartz M M; Virtanen I; Gould V E
CORPORATE SOURCE: Department of Pathology, Rush Medical College, Chicago, IL 60612.
SOURCE: VIRCHOWS ARCHIV. B, CELL PATHOLOGY INCLUDING MOLECULAR PATHOLOGY, (1993) 63 (5) 307-16. Journal code: BWO; 9316922. ISSN: 0340-6075.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930806
Last Updated on STN: 19960129
Entered Medline: 19930720

AB Frozen samples of minimal change glomerulopathy (MCG), and of membranous, segmental and diffuse lupus glomerulonephritis (MGN, SGN, DLGN) were studied to assess the distribution of tenascin (Ten), and the extradomains A and B (EDA- and **EDB**-) and **oncofetal** (Onc-) **isoforms** of cellular

fibronectin (cFn). Cryosections were immunostained by the ABC method with specific monoclonal antibodies. In MCG, mesangial Ten and EDA-cFn reactions were increased. In MGN, mesangial Ten and EDA-cFn staining was enhanced except in segmental scars; convincing reactions were seen in cases with membranous transformation; spikes stained strongly. In SGN, variably intense staining for Ten and all cFn **isoforms** was seen in glomerular necrosis, proliferation and crescents; parietal epithelium EDA-cFn staining was noted. In DLGN, strong and extensive mesangial Ten and EDA-cFn staining was seen as were focal **EDB**- and Onc-cFn reactions. Parietal cells with and without crescents stained variably with all Mabs. Obsolete glomeruli were unreactive save for rare periglomerular Ten rims. Interstitial inflammation and fibrosis in MGN, SGN and DLGN had moderate to strong Ten and EDA-cFn staining with rare traces of **EDB**- and Onc-cFn. We conclude that enhanced Ten and EDA-cFn is a potentially reversible response to glomerular injury whereas the expression of **EDB**- and Onc-cFn apparently result from necrosis and/or cellular proliferation which lead to scarring. And, while mesangial cells are the major source of these molecules, epithelial cells might also partake in their synthesis.

L13 ANSWER 46 OF 52 MEDLINE DUPLICATE 34

ACCESSION NUMBER: 93313844 MEDLINE
DOCUMENT NUMBER: 93313844 PubMed ID: 7686813
TITLE: Distribution of tenascin, cellular **fibronectins** and integrins in the normal, hyperplastic and neoplastic breast.
AUTHOR: Koukoulis G K; Howeedy A A; Korhonen M; Virtanen I; Gould V E
CORPORATE SOURCE: Department of Pathology, Rush Medical College, Chicago, Illinois 60612-3864.
SOURCE: JOURNAL OF SUBMICROSCOPIC CYTOLOGY AND PATHOLOGY, (1993 Apr) 25 (2) 285-95. Ref: 90
Journal code: CMS; 8804312. ISSN: 1122-9497.
PUB. COUNTRY: Italy
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930820
Last Updated on STN: 20000303
Entered Medline: 19930810

AB We present immunolocalization data on tenascin (Ten), and extradomains A and B (EDA-, **EDB**-) and **oncofetal** (Onc-) **isoforms** of cellular **fibronectin** (cFn),

FILE 'REGISTRY' ENTERED AT 14:25:04 ON 29 JUN 2001
L6 68 S FIBRONECTIN?/CN

FILE 'CAPLUS' ENTERED AT 14:25:28 ON 29 JUN 2001
L6 68 SEA FILE=REGISTRY ABB=ON PLU=ON FIBRONECTIN?/CN
L7 19350 SEA FILE=CAPLUS ABB=ON PLU=ON L6 OR FN OR FIBRONECTIN
L8 100 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (EDB OR (ED OR EXTRA DOMAIN)(W)B)
L9 36 SEA FILE=CAPLUS ABB=ON PLU=ON L8 AND (ONCOFOETAL OR ONCOFETAL OR FOETAL OR FETAL)
L10 25 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND (ISOFORM OR ISO FORM)

L10 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:158524 CAPLUS
DOCUMENT NUMBER: 134:220391
TITLE: Immunohistochemical localization of laminin and **fibronectin isoforms** in human placental villi
AUTHOR(S): Korhonen, Matti; Virtanen, Ismo
CORPORATE SOURCE: Helsinki University Central Hospital, Hospital for Children and Adolescents, and Department of Anatomy, Institute of Biomedicine, University of Helsinki, Helsinki, Finland
SOURCE: J. Histochem. Cytochem. (2001), 49(3), 313-322
CODEN: JHCYAS; ISSN: 0022-1554
PUBLISHER: Histochemical Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The localization of laminin .alpha.1, .alpha.2, .alpha.3, .alpha.5, .beta.1, .beta.2, and .gamma.1 chains and extradomain A- (EDA), **EDB**-, and **oncofetal fibronectin** (**Fn**) was carried out by immunohistochem. in human placental villi during placental development. The laminin .alpha.2, .alpha.5, .beta.1, .beta.2, and .gamma.1 chains were detected in the trophoblastic basement membrane (BM) at all stages of gestation, suggesting the presence of laminin-2, -4, -10, and -11 trimers. The laminin .alpha.1 chain was selectively found at sites where the villous BM was in contact with proliferating cells in trophoblastic islands or columns. EDA-**Fn**, but not other **Fn** **isoforms**, was found in the trophoblastic BM during the 1st trimester. The laminin .alpha.2, .beta.1, .beta.2, and .gamma.1 chains were detected in the villous stroma and capillaries throughout placental development, whereas the laminin .alpha.5 chain emerged distinctly during development. Extensive EDA-**Fn** immunoreactivity was found in 1st-trimester villous stroma, but distinctly fewer **Fn isoforms** were seen in the villous stroma during the later stages of gestation. The results

also suggested that, during the formation of new villi, laminins are not found in trophoblastic sprouts before the in-growth of the villous mesenchyme. Rather, laminins may be deposited at the villous epithelial-mesenchymal interface. Furthermore, the results showed that distinct changes occur in the localization of various laminin and **Fn isoforms** during the maturation of villous trophoblastic and capillary BMs.

REFERENCE COUNT: 47
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(1) Aumailley, M; J Anat 1998, V193, P1 CAPLUS
(2) Autio-Harmainen, H; Lab Invest 1991, V64, P483 CAPLUS
(4) Brown, J; J Cell Sci 1994, V107, P329 CAPLUS
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(11) Church, H; Biochem J 1998, V332, P491 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:115982 CAPLUS
TITLE: Distribution of **fibronectin isoforms** in human renal disease
AUTHOR(S): Van Vliet, Anita I.; Baelde, Hans J.; Vleming, Louis-Jean; de Heer, Emile; Bruijn, Jan Anthonie
CORPORATE SOURCE: Department of Pathology, Leiden University Medical Centre, Leiden, 2300 RC, Neth.
SOURCE: J. Pathol. (2001), 193(2), 256-262
CODEN: JPTLAS; ISSN: 0022-3417
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Fibronectin** (**FN**) is an extracellular matrix component which appears in different **isoforms**, due to alternative mRNA splicing of the ED-A, **ED-B**, and IIICS regions, and subsequent post-translational modifications. The **FN isoforms**, some of which occur specifically during **fetal** development and in fibrogenic diseases, have been reported to play a role in various biol. functions, such as regulation of the matrix assembly, adhesion, and proliferation. The contribution of these **FN isoforms** to the pathogenesis of chronic renal diseases, which are also fibrogenic disorders, is not well known. This study therefore examd. the distribution of **FN isoforms** in renal diseases by immunohistochem., with a panel of **isoform**-specific monoclonal antibodies (MAbs), applied to 63 abnormal renal biopsies and ten normal controls. Normal kidneys contained total **FN** (MAb IST4) both in the mesangial and in the interstitial extracellular matrix (ECM), but only traces of ED-A-pos. **FN**

(MAb IST9), and no **ED-B**-pos. **FN** (MAb BC1) or **oncofetal FN** (MAb FDC6) was found in normal renal tissue. All patients with renal disease demonstrated increased total **FN** staining of the interstitium and the mesangium. Periglomerular fibrotic lesions and fibrous crescents showed massive accumulation of total **FN**, whereas the amt. of total **FN** in the ECM of obsolescent glomeruli was decreased, compared with that in normal mesangial ECM. **Oncofetal** (FDC6), **EDB**-neg. (MAb IST6), ED-A-pos., and **ED-B**-pos. **FN isoforms** were found in glomerular ECM accumulations and in fibrous crescents. Tubulointerstitial fibrotic lesions predominantly contained the ED-A-pos. **FN isoform**, whereas in globally sclerotic glomeruli, predominantly **ED-B**-pos. **FN** was obsd. The expression of **FN isoforms** was similar in all renal diseases studied. These results show that in various renal diseases, **oncofetal** (FDC6) **FN** and ED-A- and **ED-B**-pos. **isoforms** of **FN** accumulate at locations of chronic lesions, independently of the etiology of the disease. The deposition of these **isoforms** in human renal tissue may play a role in the modulation of the immune response by attracting monocytes and lymphocytes to the injured kidney. Furthermore, because the **ED-B**-pos. **FN isoform** is highly susceptible to proteolytic degrdn., its accumulation may play a role in scar formation and tissue repair. **ED-B**-pos. **FN** forms a temporary scaffold supporting the cells, which can easily be cleared by proteolytic degrdn. once new tissue has been produced at the site of injury.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:580661 CAPLUS

DOCUMENT NUMBER: 133:332760

TITLE: Characterization of the expression of the alternative splicing of the ED-A, **ED-B** and V regions of **fibronectin** mRNA in bovine ovarian follicles and corpora lutea

AUTHOR(S): De Candia, L. M.; Rodgers, R. J.
CORPORATE SOURCE: Department of Medicine, Flinders University of South Australia, Bedford Park, SA 5042, Australia
SOURCE: Reprod., Fertil. Dev. (1999), 11(6), 367-377
CODEN: RFDEEH; ISSN: 1031-3613
PUBLISHER: CSIRO Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Fibronectin** is an extracellular matrix glycoprotein. Alternative splicing of **fibronectin** mRNA within three specific regions, the extra domains (ED) A and B and the variable (V) or IIICS region, result in the prodn. of different **isoforms** of **fibronectin**. These **isoforms** differentially regulate tissue developmental processes, such as those occurring during follicular and luteal development. The specific **isoforms** of **fibronectin** present in follicles and corpora lutea have not been identified. To identify these, primers for reverse transcription polymerase chain reaction (RT-PCR) were designed to the known bovine amino acid sequence of exons flanking the ED-A, **ED-B** and V regions. PCR products from bovine **fetal** liver cDNA were detd. to be bovine **fibronectin** by the correct product size and DNA sequence homol. to other species, and to the known bovine amino acid sequence. Bovine ovarian follicles (0.5-9 mm diam.) and corpora lutea (cyclic, early to late mid-luteal phase) were shown to express ED-A+, ED-A-, **ED-B+**, **ED-B-**, V+ and V- **fibronectin isoforms**, similar to the liver, lung and kidney of fetuses, but generally not of adult animals. Thus follicles and corpora lutea express **isoforms** of **fibronectin** usually expressed in developing tissues.
IT **303817-87-0 303817-88-1 304014-01-5**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; bovine ovarian follicles and corpora lutea express **fibronectin** mRNA splice variants similar to those expressed in **fetal** tissues)

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:256758 CAPLUS
DOCUMENT NUMBER: 133:29226
TITLE: Overexpression of the **oncofetal** **Fn** variant containing the EDA splice-in segment in the dermal-epidermal junction of psoriatic uninvolved skin
AUTHOR(S): Ting, Kathleen M.; Rothaupt, Dinah; McCormick, Thomas S.; Hammerberg, Craig; Chen, Guofen; Gilliam, Anita C.; Stevens, Seth; Culp, Lloyd; Cooper, Kevin D.
CORPORATE SOURCE: Departments of Dermatology and Microbiology and Molecular Biology, University Hospitals of Cleveland and VA Medical Center, Case Western Reserve University, Cleveland, OH, USA
SOURCE: J. Invest. Dermatol. (2000), 114(4), 706-711
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The extracellular matrix protein, **Fn**, has crit. functions in cell attachment, migration, differentiation, and proliferation. The authors have previously shown that **fibronectin** (**Fn**) is abnormally expressed and potentiates entry into the cell cycle of basal keratinocytes in uninvolved psoriatic skin, in combination with T cell lymphokines. It is not known what type of **Fn** is present in psoriatic skin, however, and how this **Fn** may regulate signaling. Embryonic forms of cellular **Fn** contg. extra domains, designated EDA and **EDB**, are generated by alternative splicing and are seen in proliferating, developing tissue and in wound healing. Because the EDA segment enhances the integrin binding sequence Arg, Gly, Asp (RGD), which, when present, has been shown to be crit. in integrin-extracellular matrix signaling, the authors were particularly interested in detg. whether or not EDA-contg. **Fn** (EDA+**Fn**) represented the aberrantly expressed **Fn** in psoriasis. Increased EDA+ **Fn** protein was demonstrated by immunostaining at the dermal-epidermal junction in clin. uninvolved skin from six of six patients with psoriasis, but not in skin from control subjects. Using reverse transcription polymerase chain reaction an increased ratio of EDA+ **Fn** vs. EDA- **Fn** mRNA was present in epidermal samples from psoriatic but not control individuals. Interestingly, the EDA+ **Fn** in the psoriatic epidermis had the IIICS region spliced out (EDA+, FDB-, IIICS-, III9+), which was shared with normal epidermis (EDA-, **EDB** -, IIICS-, III9+). These results suggest a selective predominance of the EDA+ **Fn isoform** at the dermal-epidermal

junction of psoriatic skin. The consistent aberrant localization of EDA+ **Fn** at the dermal-epidermal junction in uninvolved skin of psoriatics may confer the hyperresponsiveness of psoriatic uninvolved basal keratinocytes for rapid cellular proliferation in response to T cell signals.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:72244 CAPLUS

DOCUMENT NUMBER: 132:206238

TITLE: Source of **oncofetal ED-B**-containing **fibronectin**: implications of production by both tumor and endothelial cells

AUTHOR(S): Midulla, Marta; Verma, Rakesh; Pignatelli, Massimo; Ritter, Mary A.; Courtenay-Luck, Nigel S.; George, Andrew J. T.

CORPORATE SOURCE: Department of Immunology, Division of Medicine, Imperial College School of Medicine, Hammersmith Hospital, London, W12 0NN, UK

SOURCE: Cancer Res. (2000), 60(1), 164-169
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **ED-B fibronectin** (**FN**) is a **FN isoform** derived from alternative splicing of the primary transcript of a single gene. Its expression on tumor stroma and neoformed tumor vasculature and its absence, with few exceptions, in normal adult tissues imply a prognostic and diagnostic value for **ED-B FN**. We investigated the location and source of **ED-B FN** because this will be of importance both in understanding its role in tumor development and in designing strategies to target this mol. We have confirmed that **ED-B FN** is expressed in the majority of breast and colorectal carcinoma tissue samples, with strong immunohistochem. staining around the tumor cells and in the tumor stroma. No staining of tumor neovasculature was seen. **ED-B FN**

is produced by a range of tumor and endothelial (both primary and transformed) cell lines, as detected by reverse transcription-PCR, but is not expressed at the plasma membrane. Strong expression of human **ED-B FN** is seen in tumor xenografts. These data indicate that neoplastic cells can act as the source of **ED-B FN** in tumors. The lack of cell surface expression on tumor cell lines has clear implications for the design of therapeutic strategies which target this mol.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:790028 CAPLUS
DOCUMENT NUMBER: 133:15492

TITLE: Distribution of laminin and **fibronectin isoforms** in oral mucosa and oral squamous cell carcinoma

AUTHOR(S): Kosmehl, H.; Berndt, A.; Strassburger, S.; Borsi, L.; Rousselle, P.; Mandel, U.; Hyckel, P.; Zardi, L.; Katenkamp, D.
CORPORATE SOURCE: Institute of Pathology, Friedrich Schiller University, Jena, D-07740, Germany

SOURCE: Br. J. Cancer (1999), 81(6), 1071-1079
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The expression of laminin and **fibronectin isoforms** varies with cellular maturation and differentiation and these differences may well influence cellular processes such as adhesion and motility. The basement membrane (BM) of **fetal** oral squamous epithelium contains the laminin chains, .alpha.2, .alpha.3, .alpha.5, .beta.1, .beta.2, .beta.3, .gamma.1 and .gamma.2. The BM of adult normal oral squamous epithelium comprises the laminin chains, .alpha.3, .alpha.5, .beta.1, .beta.3, .gamma.1 and .gamma.2. A re-expression of the laminin .alpha.2 and .beta.2 chains could be shown in adult hyperproliferative, dysplastic and cancer lesions.

In dysplasia and oral squamous cell carcinoma (OSCC), multifocal breaks of the BM are present as indicated by laminin chain antibodies. These breaks correlate to malignancy grade in their extent. Moreover, in the invasion front the .alpha.3 and .gamma.2 chain of laminin-5 can immunohistochem. be found outside the BM within the cytoplasm of budding carcinoma cells and in the adjacent stroma. The correlation between the morphol. pattern of invasive tumor clusters and a laminin-5 immunostaining in the adjacent stroma may suggest, first, that a laminin-5 deposition outside the BM is an immunohistochem. marker for invasion and second, that OSCC invasion is guided by the laminin-5 matrix. Expression of **oncofetal fibronectins** (IIICS de novo glycosylated **fibronectin** and **ED-B fibronectin**) could be demonstrated throughout the stromal compartment. However, the **ED-B fibronectin** synthesizing cells (RNA/RNA in situ hybridization) are confined to small stroma areas and to single stroma and inflammatory cells in the invasion front. A correlation of the no. of **ED-B fibronectin** synthesizing cells to malignancy grade could not be seen. **ED-B fibronectin** mRNA-pos. cells seem to be concd. in areas of fibrous stroma recruitment with a linear alignment of stromal fibro-/myofibroblasts (desmoplasia). Double staining expts. (**ED-B fibronectin** in situ hybridization and .alpha.-smooth muscle actin immunohistochem.) indicated that the stroma myofibroblasts are a preferential source of **ED-B fibronectin**. In conclusion, in OSCC, a **fetal** extracellular matrix conversion is demonstrable. Tumor cells (laminin .alpha.2 and .beta.2 chain) and recruited stromal myofibroblasts (**oncofetal ED-B fibronectin**) contribute to the **fetal** extracellular matrix milieu.

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REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:437710 CAPLUS
DOCUMENT NUMBER: 131:211025
TITLE: A high-affinity human antibody that targets tumoral blood vessels

AUTHOR(S): Tarli, Lorenzo; Balza, Enrica; Viti, Francesca; Borsi, Laura; Castellani, Patrizia; Berndorff, Dietmar; Dinkelborg, Ludger; Neri, Dario; Zardi, Luciano

CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik, ETH Honggerberg, Zurich, CH-8093, Switz.

SOURCE: Blood (1999), 94(1), 192-198
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiogenesis is a characteristic feature of many aggressive tumors and of other relevant disorders. Mols. capable of specifically binding to new-forming blood vessels, but not to mature vessels, could be used as selective vehicles and would, therefore, open diagnostic and therapeutic opportunities. We have studied the distribution of the **ED-B oncofetal** domain of **fibronectin**, a marker of angiogenesis, in four different tumor animal models: the F9 murine teratocarcinoma, SKMEL-28 human melanoma, N592 human small cell lung carcinoma, and C51 human colon carcinoma. In all of these exptl. models we obsd. accumulation of the **fibronectin isoform** contg. the **ED-B** domain around neovascular structures when the tumors were in the exponentially growing phase, but not in the slow-growing phase. Then we performed biodistribution studies in mice bearing a s.c. implanted F9 murine teratocarcinoma, using a high-affinity human antibody fragment (L19) directed against the **ED-B** domain of **fibronectin**.

Radiolabeled L19, but not an irrelevant anti-lysozyme antibody fragment (D1.3), efficiently localizes in the tumoral vessels. The maximal dose of L19 accumulated in the tumor was obsd. 3 h after injection (8.2% injected dose per g). By virtue of the rapid clearance of the antibody fragment from the circulation, tumor-to-blood ratios of 1.9, 3.7, and 11.8 were obtained at 3, 5, and 24 h, resp. The tumor-targeting performance of L19 was not dose-dependent in the 0.7 to 10 .mu.g range of injected antibody. The integral of the radioactivity localized in tumoral vessels over 24 h was greater than 70-fold higher than the integral of the radioactivity in blood over the same time period, normalized per g of tissue or fluid. These findings quant. show that new-forming blood vessels can selectively be targeted in vivo using specific antibodies, and suggest that L19 may be of clin. utility for the immunoscintigraphic detection of angiogenesis in patients.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:274972 CAPLUS
DOCUMENT NUMBER: 131:98949
TITLE: NMR structure of the human **oncofoetal fibronectin ED-B** domain, a specific marker for angiogenesis
AUTHOR(S): Fattorusso, Roberto; Pellecchia, Maurizio; Viti, Francesca; Neri, Paolo; Neri, Dario; Wuthrich, Kurt
CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik, Eidgenossische Technische Hochschule Honggerberg, Zurich, CH-8093, Switz.
SOURCE: Structure (London) (1999), 7(4), 381-390
CODEN: STRUE6; ISSN: 0969-2126
PUBLISHER: Current Biology Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The process of angiogenesis (i.e. the formation of new blood vessels from pre-existing ones) is fundamental to physiol. processes such as reprodn., development and repair, as well as to pathol. conditions such as tumor progression, rheumatoid arthritis and ocular disorders. The **oncofoetal ED-B** domain, a specific marker of angiogenesis, consists of 91 amino acid residues that are inserted by alternative splicing into the **fibronectin** (**FN**) mol. The NMR structure of the **ED-B** domain is reported and reveals important differences from other **FN** type III domains. A comparison of the **ED-B** domain with the crystal structure of a four-domain **FN** fragment shows the novel features of **ED-B** to be located in loop regions that are buried at interdomain interfaces, and which therefore largely det. the global shape of the **FN** mol. The neg. charged amino acids in this highly acidic protein are uniformly distributed over the mol. surface, with the sole exception of a solvent-exposed hydrophobic patch that represents a potential specific recognition site. Epitope mapping with 82 decapeptides that span the **ED -B** sequence revealed that three **ED-B** -specific monoclonal antibodies, which selectively target newly forming blood vessels in tumor-bearing mice, bind to adjacent regions on the **ED-B** surface. The NMR structure enables the identification of a large surface area of the **ED -B** domain that appears to be accessible in vivo, opening

up new diagnostic and therapeutic opportunities. Furthermore, the mapping of specific monoclonal antibodies to the three-dimensional structure of the **ED-B** domain, and their use in angiogenesis inhibition expts., provides a basis for further investigation of the role of the **ED-B** domain in the formation of new blood vessels.

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:12672 CAPLUS

DOCUMENT NUMBER: 128:138090

TITLE: A pilot pharmacokinetic and immunoscintigraphic study with the technetium-99m-labeled monoclonal antibody BC-1 directed against **oncofetal fibronectin** in patients with brain tumors

AUTHOR(S): Mariani, Giuliano; Lasku, Arben; Pau, Antonio; Villa, Giuseppe; Motta, Cinzla; Calcagno, Giuseppina; Taddel, Gioconda Z.; Castellani, Patrizia; Syrigos, Kostas; Dorcaratto, Alessandra; Epenetos, Agamennon A.; Zardi, Luciano; Viale, Giuseppe A.

CORPORATE SOURCE: Nuclear Medicine Service, DIMI, University of Genoa, Genoa, I-16132, Italy

SOURCE: Cancer (N. Y.) (1997), 80(12, Suppl.), 2484-2489
CODEN: CANCAR; ISSN: 0008-543X

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Preliminary expts. in an animal model have shown the favorable tumor targeting potential in vivo of radiolabeled BC-1, an Ig (Ig)G1 monoclonal antibody (MoAb) that recognizes the human **fibronectin isoform** (B+) contg. the **ED-B oncofetal** domain. This antigen has extremely restricted distribution in normal adult tissues. Instead, it is highly expressed in **fetal** and tumor tissues, esp. in high grade astrocytomas and malignant gliomas of the brain, in which the process of neoangiogenesis linked to tumor growth is particularly

important. This study was carried out with five patients who had malignant brain tumors (four gliomas and one malignant angioblastic meningioma). The BC-1 MoAb was labeled with technetium-99m (99mTc) by MDP transchelation. Planar and single photon emission computed tomog. (SPECT) imaging was acquired at 4-6 and 20 h after i.v. injection of about 450 MBq/0.2 mg 99mTc-BC-1 and was compared with the nonspecific indicator of blood-brain barrier disruption, 99mTc-diethylenetriamine pentaacetic acid (DTPA). Plasma pharmacokinetic anal. was based on serial blood sampling. All patients underwent potentially curative surgery at the end of the study. The plasma clearance curves were biexponential, with av. T1/2 values of 2-4 h and 28-33 h, resp. 99mTc-BC-1 showed very low nonspecific uptake in the bone marrow, liver, and spleen. Planar and SPECT imaging with 99mTc-BC-1 visualized brain tumors in all patients, with a pattern of intratumor distribution that specifically identified areas of peripheral tumor growth more accurately than the nonspecific indicator, 99mTc-DPTA. Tumor uptake of 99mTc-BC-1 was correlated with the expression of the specific **oncofetal fibronectin**, as shown by immunohistochem. on surgical samples. These results indicate the diagnostic potential of MoAb 99mTc-BC-1 for immunoscintigraphy in cancer patients, at least when neoangiogenesis induced by cancer is particularly important.

L10 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:805838 CAPLUS
DOCUMENT NUMBER: 128:74309
TITLE: Antibodies to the **ED-B** domain of **fibronectin**: their construction and application
INVENTOR(S): Neri, Dario; Carnemolla, Barbara; Siri, Annalisa; Balza, Enrica; Castellani, Patrizia; Pini, Alessandro; Zardi, Luciano; Winter, Greg; Neri, Giovanni; Borsi, Laura; et al.
PATENT ASSIGNEE(S): Medical Research Council, UK; Instituto Nazionale Per La Ricerca Sul Cancro; Universita' Di Siena; Neri, Dario; Carnemolla, Barbara; Siri, Annalisa; Balza, Enrica; Castellani, Patrizia; Pini, Alessandro; et al.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9745544 A1 19971204 WO 1997-GB1412 19970523
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
CA 2256308 AA 19971204 CA 1997-2256308 19970523
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO
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NO 9805459 A 19990122 NO 1998-5459 19981123
PRIORITY APPLN. INFO.: GB 1996-10967 A 19960524
WO 1997-GB1412 W 19970523

AB The present invention discloses antibodies and antibody fragments that provide specific binding to the **ED-B oncofoetal** domain of **fibronectin**. The authors also disclose materials and methods for the prodn. of such antibodies and derived fragments.

L10 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:561507 CAPLUS
DOCUMENT NUMBER: 127:218314
TITLE: Loss of **EDB+ fibronectin isoform** is associated with differentiation of alveolar epithelial cells in human **fetal** lung
AUTHOR(S): Arai, Hirokazu; Hirano, Hisanobu; Mushiake, Sotaro; Nakayama, Masahiro; Takada, Goro; Sekiguchi, Kiyotoshi
CORPORATE SOURCE: Department of Pathobiology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan
SOURCE: Am. J. Pathol. (1997), 151(2), 403-412
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cell-matrix interactions have been shown to regulate the development of the lung, particularly airway branching and alveolarization. **Fibronectin** is the major constituent of pulmonary

extracellular matrix and exists in multiple **isoforms** arising from alternative RNA splicing. EDA and **EDB** are the two major alternatively spliced segments, the expression of which is regulated in a spatiotemporal and oncodevelopmental manner. In this study, the authors investigated immunohistochem. the distribution of the EDA- and **EDB**-contg. **fibronectin isoforms** (referred to as EDA+ **fibronectin** and **EDB+ fibronectin**, resp.) in normal and hypoplastic human lungs at different gestational ages to explore the role of these **fibronectin isoforms** in alveolarization. EDA+ **fibronectin** was expressed around the distal airspaces throughout the development of both normal and hypoplastic lungs. In contrast, the expression of **EDB+ fibronectin** was restricted to the lung with morphol. immature acinar complex, typically obsd. in normally developing lungs of <30 gestational weeks or in hypoplastic lungs. To further confirm the restricted expression of **EDB+ fibronectin** in immature acinar complex, the authors examd. the correlation of **EDB+ fibronectin** expression with that of the surfactant protein SP-A, a biochem. marker for the differentiated type II pneumocytes. A clear inverse relationship between the immunoreactivities for **EDB+ fibronectin** and SP-A was obsd. in both control and hypoplastic lungs. Given the proposed importance of **fibronectins** in the differentiation of alveolar epithelial cells, the authors' results suggest that the **EDB** segment plays a regulatory role in the differentiation of immature acinar epithelial cells into type II pneumocytes. The **EDB** segment may also serve as a new histochem. marker for the functional maturity of **fetal** lung tissues.

L10 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:272557 CAPLUS
DOCUMENT NUMBER: 126:328729
TITLE: The distribution of laminins and **fibronectins** is modulated during extravillous trophoblastic cell differentiation and decidual cell response to invasion in the human placenta
AUTHOR(S): Korhonen, Matti; Virtanen, Ismo
CORPORATE SOURCE: Children's Hospital, University Hospital, University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: J. Histochem. Cytochem. (1997), 45(4), 569-581
CODEN: JHCYAS; ISSN: 0022-1554
PUBLISHER: Histochemical Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The distribution of laminin (Ln) .alpha.1-.alpha.3, .beta.1-.beta.3, and .gamma.1 chains, and of the extradomain-A (EDA) and -B (**EDB**) and the **oncofetal** epitope of **fibronectin** (Onc-**Fn**) in extravillous trophoblastic cells and decidua in the human placenta was detd. by immunohistochem. It was found that the transition from villous to extravillous trophoblast was accompanied by emergence of immunoreactivity for EDA-, **EDB**-, and Onc-**Fn** among the cells. Furthermore, whereas the villous trophoblastic basement membrane (BM) contained Ln .alpha.1, .alpha.2, .beta.1, .beta.2, and .gamma.1 chains, immunoreactivity for Ln .alpha.1, .beta.1, and .gamma.1, but not for Ln .alpha.2 and .beta.2 chains, was detected in assocn. with extravillous trophoblastic cells. Interestingly, although immunoreactivity for the Ln .alpha.1, .alpha.2, .beta.1, .beta.2, and .gamma.1 chains was detected in all decidual cell BMs, **EDB**-**Fn** and Onc-**Fn** were detected only in decidua that had been invaded by the trophoblast. In summary, the results describe distinct changes in the distribution of Ln and **Fn isoforms** during the differentiation of villous trophoblast into extravillous trophoblastic cells. Furthermore, **EDB**- and Onc-**Fn** are preferentially found in decidua that has been invaded by the trophoblast, indicating that the deposition of these **Fn isoforms** reflects a decidual cell response to invasion.

L10 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:742686 CAPLUS
DOCUMENT NUMBER: 126:17591
TITLE: Phage antibodies with pan-species recognition of the **oncofetal** angiogenesis marker **fibronectin ED-B** domain
AUTHOR(S): Carnemolla, Barbara; Neri, Dario; Castellani, Patrizia; Leprini, Alessandra; Neri, Giovanni; Pini, Alessandro; Winter, Greg; Zardi, Luciano
CORPORATE SOURCE: Laboratory Cell Biology, Instituto Nazionale per la Ricerca sul Cancro, Genoa, 16132, Italy
SOURCE: Int. J. Cancer (1996), 68(3), 397-405
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Fibronectin** (**FN**) exists in several polymorphic forms due to alternative splicing. The B-**FN** **isoform** (with **ED-B** domain inserted by splicing) is present in the stroma of **fetal** and neoplastic tissues and in adult and neoplastic blood vessels during angiogenesis but is undetectable in mature vessels. This

isoform, therefore, represents a promising marker for angiogenesis, as already shown using the mouse monoclonal antibody (MAb) BC-I directed against an epitope on human B-**FN**. However, this MAb does not directly recognize the human **ED-B** domain nor does it recognize B-**FN** of other species; therefore, it cannot be used as a marker of angiogenesis in animal models. In principle, antibodies directed against the human **ED-B** domain should provide pan-species markers for angiogenesis as the sequence of this domain is highly conserved in different species (and identical in humans and mice). As it has proved difficult to obtain such antibodies by hybridoma technol., we used phage display technol. Here, we describe the isolation of human antibody fragments against the human **ED-B** domain that bind to human, mouse and chicken B-**FN**. As shown by immunohistochem., the antibody fragments stain human neoplastic tissues and the human, mouse and chicken neovasculature.

L10 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:60083 CAPLUS
DOCUMENT NUMBER: 124:172050
TITLE: Specific expression of the **ED-B** containing **fibronectin isoform** by endothelial cells of growing tumor vessels
AUTHOR(S): Castellani, Patrizia; Viale, Giuseppe; Dorcaratto, Alessandra; Querze, Germano; Allemanni, Giorgio; Zardi, Luciano; Siri, Annalisa
CORPORATE SOURCE: Lab. Cell. Biol., Inst. Nazionale per la Ricerca sul Cancro, Genoa, Italy
SOURCE: Antibody, Immunoconjugates, Radiopharm. (1995), 8(4), 325-32
CODEN: AIRAEB; ISSN: 0892-7049
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **fibronectin** (**FN**) **isoform** contg. the **ED-B** sequence (B+**FN**) shows an extremely restricted distribution in normal adult tissues, while it is highly expressed in **fetal** and tumor tissues. Using the monoclonal antibody (mAb) BC-1, specific for this **FN isoform**, we demonstrate here, using immunohistochem. techniques, that B+**FN** is undetectable in mature vessels and, vice versa, that it is highly expressed during angiogenesis in neoplastic tissues. B+**FN** is thus a marker of new vessel formation in tumors, and the mAb BC-1 may be a useful reagent to evaluate the level of angiogenetic processes in different neoplasia.

L10 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:3789 CAPLUS
DOCUMENT NUMBER: 124:113962
TITLE: Tenascin and **fibronectin** **isoforms** in human renal cell carcinomas, renal cell carcinoma cell lines and xenografts in nude mice
AUTHOR(S): Lohi, Jouni; Tani, Taneli; Laitinen, Liisa; Kangas, Lauri; Lehto, Veli-Pekka; Virtanen, Ismo
CORPORATE SOURCE: Institute Biomedicine, University Helsinki, Helsinki, FIN-00014, Finland
SOURCE: Int. J. Cancer (1995), 63(3), 442-9
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the expression of tenascin (Tn) and **isoforms** of **fibronectin** (**Fn**) in human renal cell carcinomas (RCC) and oncocytomas, in RCC cell lines and in their s.c. implanted xenografts in nude mice. In well-differentiated RCCs and oncocytomas, extra-domain A (EDA)-**Fn** and Tn immunoreactivities were confined to the basement membranes and blood vessels, while in less-differentiated RCCs they were also widely seen in the stroma, correlating with the morphol. differentiation of the tumor. Expression of **EDB-Fn** and **oncofetal** (onc)-**Fn** was very scarce in most of the RCCs and oncocytomas. Western blotting results demonstrated the predominance of the Mr 190,000 Tn subunit in most RCCs. Among the 4 RCC cell lines, 3 showed Tn in the extracellular matrix. As xenografts, they formed moderately or poorly differentiated tumors, with abundant Tn. Three of the RCC cell lines also showed secretion of EDA-**Fn** and 2 of them secretion of onc-**Fn** and **EDB-Fn** into the culture medium, while in xenografts there was a strong expression of all **Fn** **isoforms**. In xenografts, the expression of Tn closely recapitulated that seen in clin. tumors and in the cell lines in vitro, while the expression of **Fn isoforms** in cultured cells and their xenografts was highly discordant.

L10 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:915633 CAPLUS
DOCUMENT NUMBER: 123:330749
TITLE: Transforming growth factor-.beta. regulates the expression of **fibronectin** and tenascin in BEAS 2B human bronchial epithelial cells
AUTHOR(S): Linnala, Auli; Kinnula, Vuokko; Laitinen, Lauri A.; Lehto, Veli-Pekka; Virtanen, Ismo
CORPORATE SOURCE: Dep. Anatomy, Univ. Helsinki, Helsinki, Finland
SOURCE: Am. J. Respir. Cell Mol. Biol. (1995), 13(5), 578-85

CODEN: AJRBEL; ISSN: 1044-1549
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors used monoclonal antibodies to study expression and extracellular matrix (ECM) incorporation of tenascin (Tn) and **isoforms** of **fibronectin** (**Fn**) in BEAS 2B immortalized human bronchial epithelial cells and the regulation of their synthesis by transforming growth factor (TGF)-.beta.1 and -.beta.2. In immunofluorescence microscopy, the control cells appeared neg. for Tn. Extradomain A (EDA)-**Fn** was mainly seen in assocn. with ECM fibers and, in a few cells, in an intracellular location. Immunoreactivity for **oncofetal** (onc)-**Fn** and extradomain B (**EDB**)-**Fn** was only seen in a few cells. In TGF-.beta.1- and -.beta.2-treated cells, a greatly enhanced immunostaining for Tn and 3 **isoforms** of **Fn** was seen both as to the no. of pos. cells and to the amt. of immunoreactive material around them. In Western blotting of the untreated cells, EDA-**Fn** and onc-**Fn** were detected in the cell-free ECM and in the culture medium, whereas **EDB-Fn** was not detectable. An enhanced secretion and deposition of both EDA-**Fn** and onc-**Fn** and also secretion of **EDB-Fn** was seen upon treatment with TGF-.beta.s. In TGF-.beta.-treated cells, Tn was found exclusively in the ECM and not in the culture medium as shown by Western blotting of cell-free ECM and culture medium, resp. Accentuation of tenascin staining in TGF-.beta.-treated cells was due to a greatly enhanced prodn. of Mr 280,000 and Mr 190,000 **isoforms** of Tn. Also, Northern blotting demonstrated a much higher level of message for both Tn and **Fn** after exposure to TGF-.beta., suggesting either a transcriptional activation or an extended half-life of the message.

L10 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:467263 CAPLUS
DOCUMENT NUMBER: 122:236076
TITLE: Chondrocyte heterogeneity: immunohistologically defined variation of integrin expression at different sites in human **fetal** knees
AUTHOR(S): Salter, Donald M.; Godolphin, Jane L.; Gourlay, Market S.
CORPORATE SOURCE: Dep. Pathol., Edinburgh Univ., Edinburgh, EH8 9AG, UK
SOURCE: J. Histochem. Cytochem. (1995), 43(4), 447-57
CODEN: JHCYAS; ISSN: 0022-1554
DOCUMENT TYPE: Journal
LANGUAGE: English

AB During development and at maturity different forms of cartilage vary in morphol. and macromol. content. This reflects heterogeneity of

chondrocyte activity, in part involving differential interactions with the adjacent extracellular matrix via specialized cell surface receptors such as integrins. We undertook an immunohistol. study on a series of human **fetal** knee joints to assess variation in the expression of integrins by chondrocytes and potential matrix ligands in articular, epiphyseal, growth plate, and meniscal cartilage. The results show that articular chondrocytes (.beta.1+, .beta.5.alpha.V+, .alpha.1+, .alpha.2+/-, .alpha.5+, weakly .alpha.6+, .alpha.V+) differed from epiphyseal (.beta.1+, .beta.5.alpha.V+, .alpha.1-, .alpha.2-, .alpha.5+, .alpha.6+, .alpha.V+), and meniscal cells (.beta.1+, .beta.5.alpha.V+, .alpha.1+, strongly .alpha.2+, .alpha.5+, .alpha.6+, .alpha.V+) in expression of integrin subunits. There was no expression of .beta.3, .beta.4, .beta.6, or .alpha.3 by chondrocytes. These results differ from previous reports on the expression of integrins by adult articular cartilage, where .alpha.2 and .alpha.6 are not seen. Variation in distribution of matrix ligands was also seen. **Fibronectin**, laminin and Type VI collagen were expressed in all cartilages but there was restricted expression of tenascin, ED-A and **ED-B fibronectin isoforms** (articular cartilage and meniscus), and vitronectin (absent from growth plate cartilage). Regulated expression of integrins by chondrocytes, assocd. with changes in the pericellular matrix compn., is of potential importance in control of cartilage differentiation and function in health and disease.

L10 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:10509 CAPLUS
DOCUMENT NUMBER: 122:2010
TITLE: RT-PCR detection of **fibronectin** EDA+ and **EDB**+ mRNA **isoforms**: Molecular markers for hepatocellular carcinoma
AUTHOR(S): Tavian, Daniela; De Petro, Giuseppina; Colombi, Marina; Portolani, Nazario; Giulini, Stefano Maria; Gardella, Rita; Barlati, Sergio
CORPORATE SOURCE: Dep. Biomed. Sci. and Biotechnol., Univ. Brescia, Brescia, 25123, Italy
SOURCE: Int. J. Cancer (1994), 56(6), 820-5
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alternative splicing of **fibronectin** (**FN**) pre-mRNA has been shown to be independently regulated at the EDA and **EDB** regions in a tissue and developmental stage-specific manner. In this study, RT-PCR approaches were developed for the detection of EDA and **EDB FN** mRNA **isoforms** in hepatocarcinoma cells (SK-Hep-1) grown in vitro and in human liver biopsies. While EDA+ and **EDB**+

isoforms were not present in control adult liver, they were detectable in the hepatocarcinoma cells and in **fetal** liver. The RT-PCR anal., extended to biopsies of malignant and nonmalignant hepatic tissues, showed that **FN** mRNAs contg. the EDA and **EDB** sequences were present in the 14 hepatocellular carcinomas (HCCs) tested but absent in the nontumorous liver tissues (i.e., normal parenchyma, nonspecific reactive and chronic hepatitis, steatosis). The **EDB+** **FN** mRNA **isoforms** were also detected in 3 cases of benign neoplasm (hepatocellular adenoma, 1; nodular focal hyperplasia (NFH) 2), whereas the EDA+ was only detectable in 1 of the 2 cases of NFH. In addn., both EDA+ and **EDB+** **isoforms** were expressed in 5 out of 9 cirrhotic livers surrounding the tumors. This mol. anal., which can also be performed on small liver biopsies (2 mg), may therefore be a useful addnl. tool in the diagnosis of HCC.

L10 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:159575 CAPLUS
DOCUMENT NUMBER: 120:159575
TITLE: **Isoforms** of cellular **fibronectin** and tenascin in amniotic fluid
AUTHOR(S): Linnala, Auli; von Koskull, Harriet; Virtanen, Ismo
CORPORATE SOURCE: Department of Anatomy, University of Helsinki, PO Box 9, Siltavuorenpenger 20 A, FIN-00014 University of Helsinki, Helsinki, Finland
SOURCE: FEBS Lett. (1994), 337(2), 167-70
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amniotic fluid (AF) obtained from 2nd trimester pregnancies presented extradomain (ED) A, B and an **oncofetal** (onc-f) domain contg. **isoforms** of cellular **fibronectin** (cFn) in Western blotting of gelatin-bound polypeptides and directly of AF. Western blotting after sequential immunopptn. suggested .gtoreq.3 **Fn** mols.: 1 contg. EDA and the onc-f domain and another minor component distinctly contg. all the domains, and a 3rd only contg. EDA. The immunoblotting results for EDA-cFn and onc-f-cFn were closely similar to that for total **Fn**, whereas in plasma samples of normal and pregnant women only traces of EDA-cFn and onc-f-cFn, but no **EDB**-cFn, were found. Western blotting of AF also indicated the presence of 3 **isoforms** of tenascin (Tn), Mr 190,000 and 280,000 polypeptides earlier found in many cells, and a Mr 200,000 polypeptide, novel for AF and not present in plasma. The results suggest a novel extracellular matrix polypeptide compn. for AF.

L10 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:446494 CAPLUS
DOCUMENT NUMBER: 119:46494
TITLE: Coordinate oncodevelopmental modulation of alternative splicing of **fibronectin** pre-messenger RNA at ED-A, **ED-B**, and CS1 regions in human liver tumors
AUTHOR(S): Oyama, Fumitaka; Hirohashi, Setsuo; Sakamoto, Michiie; Titani, Koiti; Sekiguchi, Kiyotoshi
CORPORATE SOURCE: Inst. Compr. Med. Sci., Fujita Health Univ., Toyoake, 470-11, Japan
SOURCE: Cancer Res. (1993), 53(9), 2005-11
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mol. diversity of **fibronectin** arises from alternative RNA splicing at regions termed ED-A, **ED-B**, and IIICS. The splicing patterns of **fibronectin** pre-mRNA at both **ED-B** and IIICS regions in various human liver tissues was investigated with an emphasis on the expression of the alternative cell adhesive site CS1 within the IIICS region. The relative abundance of the **fibronectin** mRNA contg. the CS1 sequence was increased in both **fetal** and cancerous liver tissues, although it was not affected in nonmalignant tissues with chronic hepatitis and cirrhosis. Similarly, the relative abundance of the **fibronectin** mRNA contg. the **ED-B** region was also increased in both **fetal** liver and liver tumors, showing a close parallelism with the splicing pattern at the ED-A region. Immunohistochem. examn. of cancerous liver tissues with monoclonal antibodies directed to the ED-A and **ED-B** segments revealed that the **fibronectin isoforms** contg. these extra peptide segments were specifically deposited in the tumor nodules. Other genes encoding kininogen, .gamma. chain of fibrinogen, and .beta.-amyloid protein precursor, all of which had been shown to be alternatively processed, did not show any significant alteration in the splicing pattern in cancerous liver tissues. Thus, the alternative splicing of **fibronectin** pre-mRNA at the ED-A, **ED-B**, and IIICS regions is coordinately modulated in both **fetal** and cancerous liver tissues toward inclusion of the extra peptide segments, and only certain selected genes are susceptible for "fine tuning" of alternative RNA splicing in cancerous liver tissues.

L10 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:121543 CAPLUS
DOCUMENT NUMBER: 118:121543

TITLE: Human amnion epithelial cells assemble tenascins and three **fibronectin isoforms** in the extracellular matrix

AUTHOR(S): Linnala, Auli; Balza, Enrica; Zardi, Luciano; Virtanen, Ismo

CORPORATE SOURCE: Dep. Anat., Univ. Helsinki, Siltavuorenpenger 20 A, Helsinki, 00170, Finland

SOURCE: FEBS Lett. (1993), 317(1-2), 74-8
CODEN: FEBLAL; ISSN: 0014-5793

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Monoclonal antibodies (MAb) were used to show that cultured human amnion epithelial (HuA) cells produce tenascins (Tn) and **isoforms** of cellular **fibronectin** (cFn). Tn polypeptides of Mr 280,000 and 190,000, assembled into extracellular matrix (ECM) but not secreted into the culture medium by HuA cells, were electrophoretically similar to those produced by human fibroblasts as revealed with domain-specific MAbs. The results suggested that most **Fn** produced by HuA cells contained the extradomain (ED) A and an **oncofetal** domain but only a minor fraction **EDB**. In immunofluorescence Tn and **Fn** were seen in different cytoplasmic granules upon monensin-induced intracellular accumulation. Tn appeared to be deposited in the ECM in colocalization with **Fn** but distinctly slower. The present results show that cultured normal human epithelial cells synthesize Tn and three **isoforms** of cFn and secrete them by using different cytoplasmic pathways.

L10 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:568857 CAPLUS

DOCUMENT NUMBER: 117:168857

TITLE: Differential distribution of tenascin and cellular **fibronectins** in acute and chronic renal allograft rejection

AUTHOR(S): Gould, Victor E.; Martinez-Lacabe, Viviana; Virtanen, Ismo; Sahlin, Karin M.; Schwartz, Melvin M.

CORPORATE SOURCE: Dep. Pathol., Ruch Med. Coll., Chicago, IL, USA

SOURCE: Lab. Invest. (1992), 67(1), 71-9
CODEN: LAINAW; ISSN: 0023-6837

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Acute and chronic renal allograft rejection injuries involve, albeit variably, all compartments of the organ and are assocd. with significant structural changes. The authors hoped to gain new insights into these phenomena by detg. distribution of certain extracellular matrix proteins known to be involved in architectural remodeling processes. Frozen tissue samples from biopsies of acute

(n = 14) and chronic (n = 12) human renal allograft rejections were studied to compare distribution of tenascin, the extradomains A and B (EDA, **EDB**), and **oncofetal** (Onc) **isoforms** of cellular **fibronectin** (cFn). Normal kidneys (n = 4) served as controls. Cryosections were immunostained by the avidin-biotin-complex method with monoclonal antibodies specific for those mols. In acute rejection, reactivity for tenascin and EDA-CFn was increased slightly to moderately in glomerular mesangia and in most vessels while it was intensely and diffusely increased in the interstitium. Rarely were focal **EDB**-cFn and Onc-cFn reactions seen in lesions deemed to reflect acute injury. In chronic rejection, tenascin and EDA-CFn were strongly increased in most glomerular mesangia and in vascular walls but unevenly in the interstitium. In rare glomerular synechiae and vessels, enhanced staining for tenascin and EDA-cFn as well as **EDB**-cFn and Onc-cFn was noted while in obsolete glomeruli only **EDB**-cFn and Onc-cFn were detected. The enhanced distribution of tenascin and EDA-CFn partly reflected that noted during nephrogenesis, whereas staining patterns for **EDB**-cFn and Onc-cFn differed from their **fetal** counterparts. Tenascin and EDA-cFn are strongly and preferentially expressed in the interstitial and vascular compartments of acute and chronic renal rejection injury suggesting that, in these sites, active repair and remodeling occur during both phases of the rejection process irresp. of the changes seen by conventional microscopy. Tenascin, EDA-cFn as well as **EDB**-cFn and Onc-cFn are all involved, albeit variably, in the glomerular and vascular alterations of chronic rejection. The finding of tenascin and of the three **isoforms** of cFn in glomerular synechiae with actively proliferating epithelium suggests that certain epithelial cells might partake in the synthesis of these mols.

L10 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:125662 CAPLUS
DOCUMENT NUMBER: 116:125662
TITLE: Differential expression of the **fibronectin isoform** containing the **ED-B oncofetal** domain in normal human fibroblast cell lines originating from different tissues
AUTHOR(S): Borsi, Laura; Balza, Enrica; Allemanni, Giorgio; Zardi, Luciano
CORPORATE SOURCE: Lab. Cell Biol., Ist. Naz. Ric. Cancro, Genoa, 16132, Italy
SOURCE: Exp. Cell Res. (1992), 199(1), 98-105
CODEN: ECREAL; ISSN: 0014-4827
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Fibronectin** (**FN**) polymorphism is due both to alternative splicing of three sequences (ED-A, **ED-B**, and IIICS) of the primary transcript and to post-translational modifications. The **FN isoform** contg. the **ED-B** sequence (B-**FN**), while having an extremely restricted distribution in normal adult tissues, has a high expression in **fetal** and tumor tissues. On a panel of nonfetal skin, **fetal** skin, and **fetal** lung fibroblast cell lines, the expression of the **ED-B**-contg. **FN** mRNA (using S1-nuclease protection anal.) as well as the expression of the **ED-B** -contg. **FN isoform** (using domain-specific monoclonal antibodies) were studied. The results show that the expression of B-**FN** in the different fibroblast cell lines has an extremely great variability depending on the development stage of the donor and on the tissue of origin. Moreover, SV-40-transformed fibroblasts present a higher expression of B-**FN** mRNA with respect to their normal counterparts. An increase in the relative amt. of the B-**FN isoform** in normal human fibroblasts was also obtained by treatment with transforming growth factor-.beta..

L10 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:426901 CAPLUS
DOCUMENT NUMBER: 115:26901
TITLE: Expression of tenascin and of the **ED-B** containing **oncofetal** **fibronectin isoform** in human cancer
AUTHOR(S): Nicolo, Guido; Salvi, Sandra; Oliveri, Gianbattista; Borsi, Laura; Castellani, Patrizia; Zardi, Luciano
CORPORATE SOURCE: Lab. Anat. Pathol., Ist. Naz. Ric. Cancro, Genoa, 16132, Italy
SOURCE: Cell Differ. Dev. (1990), 32(3), 401-8
CODEN: CDDEE8; ISSN: 0922-3371
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tenascin (TN) and the **oncofetal ED-B** contg. **fibronectin isoform** (B-**FN**) have been reported to be stromal markers of a no. of malignancies. This study investigated the distribution of TN and B-**FN** in normal adult tissues and in benign and malignant tumors, as well as the levels of the B-**FN** mRNA in cultured **fetal** and non-**fetal** human fibroblasts originating from different tissues. B-**FN** has an extremely restricted distribution in normal adult tissues, is not expressed in benign tumors, but is greatly expressed in a high percentage of malignant tumors. On the

contrary, human TN in normal adult tissues is less restricted than what has previously been reported and it is largely expressed in a no. of both benign and malignant tumors. Moreover, great variability in the relative amt. of B-**FN** mRNA was obsd. among the 17 normal human fibroblast cell lines tested. Very low levels were found in non-**fetal** skin fibroblasts and higher levels in **fetal** lung fibroblasts. Differences were found in the relative amts. of B-**FN** mRNA between fibroblast cell lines originating from the skin and the lung of the same subject.

L10 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:171047 CAPLUS
DOCUMENT NUMBER: 110:171047
TITLE: A tumor-associated **fibronectin** **isoform** generated by alternative splicing of messenger RNA precursors
AUTHOR(S): Carnemolla, Barbara; Balza, Enrica; Siri, Annalisa; Zardi, Luciano; Nicotra, Maria Rita; Bigotti, Aldo; Natali, Pier Giorgio
CORPORATE SOURCE: Cell Biol. Lab., Ist. Naz. Ric. Cancro, Genoa, 16132, Italy
SOURCE: J. Cell Biol. (1989), 108(3), 1139-48
CODEN: JCLBA3; ISSN: 0021-9525
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Fibronectin** (**FN**) represents the mixt. of a no. of structurally different mols. (**isoforms**) whose make-up varies depending on the sources. **FN** from cultured transformed human cells has a very different **isoform** compn. with respect to its normal counterpart. In fact, SV-40-transformed WI-38VAI3 human fibroblasts produce high levels of a **FN isoform** (B-**FN**) which is very poorly expressed in their normal, WI-38, counterpart. It was recently demonstrated that the B-**FN isoform** derives from a differential splicing pattern of the **FN** primary transcript which leads, in transformed cells, to a high level expression of the exon **ED-B**. The present study reports on prodn. and characterization of a monoclonal antibody (BC-1) which recognizes an epitope within the protein sequence coded for by the **ED-B** exon. This monoclonal antibody makes it possible to carry out immunohistochem. anal. of the distribution of the **ED-B**-contg. **FN isoform** (B-**FN**) in human tissues. The results show that while in normal, adult, human tissues total **FN** has a widespread distribution, the B-**FN** **isoform** is restricted only to synovial cells, to some vessels and areas of the interstitium of the ovary, and to the myometrium. On the contrary, the B-**FN isoform**

has a much greater expression in **fetal** and tumor tissues. These results demonstrate that, in vivo, different **FN isoforms** have a differential distribution and indicate that the B-**FN isoform** may play a role in ontogenesis and oncogenetic processes.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:34:45 ON 29 JUN 2001)
L12 188 S L10
L13 52 DUP REM L12 (136 DUPLICATES REMOVED)

L13 ANSWER 1 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:139402 SCISEARCH
THE GENUINE ARTICLE: 399NT
TITLE: Targeted delivery of tissue factor to the **ED-B** domain of **fibronectin**, a marker of angiogenesis, mediates the infarction of solid tumors in mice
AUTHOR: Nilsson F; Kosmehl H; Zardi L; Neri D (Reprint)
CORPORATE SOURCE: Swiss Fed Inst Technol, Inst Pharmaceut Sci, Bldg 36 M14, Winterthurerstr 190, CH-8057 Zurich, Switzerland (Reprint); Swiss Fed Inst Technol, Inst Pharmaceut Sci, CH-8057 Zurich, Switzerland; Ist Nazl Ric Canc, Cell Biol Lab, I-161323 Genoa, Italy; Univ Jena, Inst Pathol, D-07740 Jena, Germany
COUNTRY OF AUTHOR: Switzerland; Italy; Germany
SOURCE: CANCER RESEARCH, (15 JAN 2001) Vol. 61, No. 2, pp. 711-716.
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 32

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The selective thrombosis of tumor blood vessels, leading to the starvation and subsequent death of tumor cells, is an attractive anticancer strategy. Here we report that a fusion protein, consisting of an antibody fragment specific for the **oncofoetal ED-B** domain of **fibronectin** fused to the extracellular domain of tissue factor, selectively targets tumor blood vessels in vivo. Furthermore, this fusion protein mediates the complete and selective infarction of three different types of solid tumors in mice. At the highest doses administered, complete tumor eradication was observed in 30% of the mice treated without apparent side effects, These results are of therapeutic relevance because the **ED-B** domain of **fibronectin**, a naturally occurring

marker of angiogenesis identical in mouse and man, is expressed in the majority of aggressive solid tumors but is undetectable in normal vessels and tissues.

L13 ANSWER 2 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:355171 SCISEARCH
THE GENUINE ARTICLE: 426AX
TITLE: Selective targeting of tumour neovasculature by a radiohalogenated human antibody fragment specific for the **ED-B** domain of **fibronectin**
AUTHOR: Demartis S; Tarli L; Borsi L; Zardi L; Neri D (Reprint)
CORPORATE SOURCE: Swiss Fed Inst Technol, Inst Pharmaceut Sci, Bldg 36 M14, Winterthurerstr 190, CH-8057 Zurich, Switzerland (Reprint); Swiss Fed Inst Technol, Inst Pharmaceut Sci, CH-8057 Zurich, Switzerland; Ist Nazl Ric Canc, Cell Biol Lab, I-16132 Genoa, Italy
COUNTRY OF AUTHOR: Switzerland; Italy
SOURCE: EUROPEAN JOURNAL OF NUCLEAR MEDICINE, (APR 2001) Vol. 28, No. 4, pp. 534-539.
Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA.
ISSN: 0340-6997.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 17

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Angiogenesis is a characteristic feature of many aggressive tumours and other disorders. Antibodies capable of binding to new blood vessels, but not to mature vessels, could be used as selective targeting agents for immunoscintigraphic and radioimmunotherapeutic applications. Here we show that scFv(L19), a recombinant human antibody fragment with sub-nanomolar affinity for the **ED-B** domain of **fibronectin**, a marker of angiogenesis, can be stably labelled with iodine-125 and astatine-211 with full retention of immunoreactivity, using a trimethyl-stannyl benzoate bifunctional derivative. Biodistribution studies in mice bearing two different types of tumour grafted subcutaneously, followed by ex vivo micro-autoradiographic analysis, revealed that scFv(L19) rapidly localises around tumour blood vessels, but not around normal vessels. Four hours after intravenous injection of the stably radioiodinated scFv(L19), tumour to blood ratios were 6:1 in mice bearing the F9 murine teratocarcinoma and 9:1 in mice bearing an FE8 rat sarcoma. As expected, all other organs (including kidney) contained significantly less radioactivity than the tumour. Since the **ED-B** domain of **fibronectin** has an identical sequence in mouse and man, scFv(L19) is a pan-species

antibody and the results presented here suggest clinical utility of radiolabelled scFv(L19) for the scintigraphic detection of angiogenesis in vivo. Furthermore, it should now be possible to investigate scFv(L19) for the selective delivery of At-211 to the tumour neovasculature, causing the selective death of tumour endothelial cells and tumour collapse.

L13 ANSWER 3 OF 52 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001158506 MEDLINE
DOCUMENT NUMBER: 21103141 PubMed ID: 11181734
TITLE: Immunohistochemical localization of laminin and **fibronectin isoforms** in human placental villi.
AUTHOR: Korhonen M; Virtanen I
CORPORATE SOURCE: Helsinki University Central Hospital, Hospital for Children and Adolescents, Helsinki, Finland.
SOURCE: JOURNAL OF HISTOCHEMISTRY AND CYTOCHEMISTRY, (2001 Mar) 49 (3) 313-22.
Journal code: IDZ; 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010222
Entered Medline: 20010322

AB We studied the localization of laminin alpha1, alpha2, alpha3, alpha5, beta1, beta2, and gamma1 chains and extradomain A- (EDA), **EDB**-, and **oncofetal fibronectin** by immunohistochemistry in human placental villi during placental development. The laminin alpha2, alpha5, beta1, beta2, and gamma1 chains were detected in the trophoblastic basement membrane (BM) at all stages of gestation, suggesting the presence of laminin-2, -4, -10, and -11 trimers. The laminin alpha1 chain was selectively found at sites where the villous BM was in contact with proliferating cells in trophoblastic islands or columns. EDA-**Fn**, but not other **Fn isoforms**, was found in the trophoblastic BM during the first trimester. The laminin alpha2, beta1, beta2, and gamma1 chains were detected in the villous stroma and capillaries throughout placental development, while the laminin alpha5 chain emerged distinctly during development. Extensive EDA-**Fn** immunoreactivity was found in first-trimester villous stroma, but distinctly fewer **Fn isoforms** were seen in the villous stroma during the later stages of gestation. Our results also suggest that, during the formation of new villi, laminins are not found in trophoblastic sprouts before the ingrowth

of the villous mesenchyme. Rather, laminins may be deposited at the villous epithelial-mesenchymal interface. Furthermore, the results show that distinct changes occur in the localization of various laminin and **Fn isoforms** during the maturation of villous trophoblastic and capillary BMs.

L13 ANSWER 4 OF 52 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001156214 MEDLINE
DOCUMENT NUMBER: 21104387 PubMed ID: 11180174
TITLE: Distribution of **fibronectin isoforms** in human renal disease.
AUTHOR: Van Vliet A; Baelde H J; Vleming L J; de Heer E; Bruijn J A
CORPORATE SOURCE: Department of Pathology, Leiden University Medical Centre, Leiden, The Netherlands.. AvVliet@Pat.AZL.nl
SOURCE: JOURNAL OF PATHOLOGY, (2001 Feb) 193 (2) 256-62. Journal code: JLB; 0204634. ISSN: 0022-3417.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered PubMed: 20010222
Entered Medline: 20010322

AB **Fibronectin** (**FN**) is an extracellular matrix component which appears in different **isoforms**, due to alternative mRNA splicing of the ED-A, **ED-B**, and IIICS regions, and subsequent post-translational modifications. The **FN isoforms**, some of which occur specifically during **fetal** development and in fibrogenic diseases, have been reported to play a role in various biological functions, such as regulation of the matrix assembly, adhesion, and proliferation. The contribution of these **FN isoforms** to the pathogenesis of chronic renal diseases, which are also fibrogenic disorders, is not well known. This study therefore examined the distribution of **FN isoforms** in renal diseases by immunohistochemistry, with a panel of **isoform**-specific monoclonal antibodies (MAbs), applied to 63 abnormal renal biopsies and ten normal controls. Normal kidneys contained total **FN** (MAb IST4) both in the mesangial and in the interstitial extracellular matrix (ECM), but only traces of ED-A-positive **FN** (MAb IST9), and no **ED-B**-positive **FN** (MAb BC1) or **oncofetal FN** (MAb FDC6) was found in normal renal tissue. All patients with renal disease demonstrated increased total **FN** staining of the interstitium and the mesangium. Periglomerular fibrotic lesions and

fibrous crescents showed massive accumulation of total **FN**, whereas the amount of total **FN** in the ECM of obsolescent glomeruli was decreased, compared with that in normal mesangial ECM. **Oncofetal** (FDC6), **EDB**-negative (MAb IST6), ED-A-positive, and **ED-B**-positive **FN isoforms** were found in glomerular ECM accumulations and in fibrous crescents. Tubulointerstitial fibrotic lesions predominantly contained the ED-A-positive **FN isoform**, whereas in globally sclerotic glomeruli, predominantly **ED-B**-positive **FN** was observed. The expression of **FN isoforms** was similar in all renal diseases studied. These results show that in various renal diseases, **oncofetal** (FDC6) **FN** and ED-A- and **ED-B**-positive **isoforms** of **FN** accumulate at locations of chronic lesions, independently of the aetiology of the disease. The deposition of these **isoforms** in human renal tissue may play a role in the modulation of the immune response by attracting monocytes and lymphocytes to the injured kidney. Furthermore, because the **ED-B**-positive **FN isoform** is highly susceptible to proteolytic degradation, its accumulation may play a role in scar formation and tissue repair. **ED-B**-positive **FN** forms a temporary scaffold supporting the cells, which can easily be cleared by proteolytic degradation once new tissue has been produced at the site of injury.

L13 ANSWER 5 OF 52 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000213485 MEDLINE
DOCUMENT NUMBER: 20213485 PubMed ID: 10733677
TITLE: Overexpression of the **oncofetal Fn** variant containing the EDA splice-in segment in the dermal-epidermal junction of psoriatic uninvolved skin.
AUTHOR: Ting K M; Rothaupt D; McCormick T S; Hammerberg C; Chen G; Gilliam A C; Stevens S; Culp L; Cooper K D
CORPORATE SOURCE: Departments of Dermatology and Microbiology and Molecular Biology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio 44106-5028, USA.
CONTRACT NUMBER: KO8AR02063 (NIAMS)
RO1AR41707 (NIAMS)
T32AR07569 (NIAMS)
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (2000 Apr) 114 (4) 706-11.
Journal code: IHZ; 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000601

AB The extracellular matrix protein, **Fn**, has critical functions in cell attachment, migration, differentiation, and proliferation. We have previously shown that **fibronectin** (**Fn**) is abnormally expressed and potentiates entry into the cell cycle of basal keratinocytes in uninvolved psoriatic skin, in combination with T cell lymphokines. It is not known what type of **Fn** is present in psoriatic skin, however, and how this **Fn** may regulate signaling. Embryonic forms of cellular **Fn** containing extra domains, designated EDA and **EDB** , are generated by alternative splicing and are seen in proliferating, developing tissue and in wound healing. Because the EDA segment enhances the integrin binding sequence Arg, Gly, Asp (RGD), which, when present, has been shown to be critical in integrin-extracellular matrix signaling, we were particularly interested in determining whether or not EDA-containing **Fn** (EDA+**Fn**) represented the aberrantly expressed **Fn** in psoriasis. Increased EDA+ **Fn** protein was demonstrated by immunostaining at the dermal-epidermal junction in clinically uninvolved skin from six of six patients with psoriasis, but not in skin from control subjects. Using reverse transcription polymerase chain reaction an increased ratio of EDA+ **Fn** versus EDA- **Fn** mRNA was present in epidermal samples from psoriatic but not control individuals. Interestingly, the EDA+**Fn** in the psoriatic epidermis had the IIICS region spliced out (EDA+, FDB-, IIICS-, III9+), which was shared with normal epidermis (EDA-, **EDB**-, IIICS-, III9+). These results suggest a selective predominance of the EDA+ **Fn isoform** at the dermal-epidermal junction of psoriatic skin. The consistent aberrant localization of EDA+ **Fn** at the dermal-epidermal junction in uninvolved skin of psoriatics may confer the hyperresponsiveness of psoriatic uninvolved basal keratinocytes for rapid cellular proliferation in response to T cell signals. Key words: immunohistochemistry/integrin/keratinocyte/RT-PCR.

L13 ANSWER 6 OF 52 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000277383 MEDLINE
DOCUMENT NUMBER: 20277383 PubMed ID: 10819258
TITLE: The angiogenesis marker **ED-B+** **fibronectin isoform** in intracranial meningiomas.
AUTHOR: Castellani P; Dorcaratto A; Pau A; Nicola M; Siri A; Gasparetto B; Zardi L; Viale G
CORPORATE SOURCE: DI.S.C.A.T Department of Surgery, University of Genoa

Medical School, Italy.
SOURCE: ACTA NEUROCHIRURGICA, (2000) 142 (3) 277-82.
Journal code: 19C; 0151000. ISSN: 0001-6268.
PUB. COUNTRY: Austria
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000724

AB **Fibronectins** (**FNs**), adhesive glycoproteins mainly expressed in the extracellular matrix, are polymorphic molecules whose various **isoforms** are dependent on alternative splicing patterns. The **isoform** containing the **ED-B** sequence and occurring in **foetal** and neoplastic tissues (**oncofoetal** or B+**FN**) has been previously recognized as a marker for angiogenesis. The distribution of this **isoform** was analyzed in a consecutive series of 134 surgically obtained intracranial meningiomas, using specific monoclonal antibodies. **Oncofoetal FN** was found to be widely distributed in the vessels of anaplastic meningiomas, with its expression being restricted in the vasculature of the typical subtypes. and absent in the neighbouring cerebral tissue. The ubiquitous vascular expression of B+**FN** in meningiomatous malignancies might provide a potential target for the in vivo delivery of angiosuppressive agents.

L13 ANSWER 7 OF 52 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001016883 MEDLINE
DOCUMENT NUMBER: 20346611 PubMed ID: 10890557
TITLE: Salivary **oncofoetal fibronectin** and oral squamous cell carcinoma.
AUTHOR: Lyons A J; Cui N
CORPORATE SOURCE: Department of Oral and Maxillofacial Surgery, King's College Hospital, London, UK.
SOURCE: JOURNAL OF ORAL PATHOLOGY AND MEDICINE, (2000 Jul) 29 (6) 267-70.
Journal code: JRF. ISSN: 0904-2512.
PUB. COUNTRY: Denmark
(EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001018

Entered Medline: 20001106

AB **Fibronectin** (**FN**) is a multifunctional adhesive glycoprotein that exists in the extracellular matrix and body fluids. As a result of alternative splicing, extra segments (ED-A and **ED-B**) may be included in the **fibronectin** molecule. These **isoforms** of **FN**, together with **FN** that has an extra glycosylation (OFFN), are strongly associated with a number of tumours, including oral squamous cell carcinoma (SCC). In view of the likely exfoliation of these cells into the oral cavity from tumours, OFFN might be present in saliva. As such, the presence of OFFN in saliva may be an indicator of oral SCC. The saliva of 12 patients with oral squamous carcinoma and 8 disease-free individuals was measured for OFFN using an enzyme-linked immunoassay. Salivary OFFN levels were similar for patients both with oral SCC and those without, suggesting that this would not be a useful test for the detection of oral SCC.

L13 ANSWER 8 OF 52 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000110789 MEDLINE
DOCUMENT NUMBER: 20110789 PubMed ID: 10646869
TITLE: Source of **oncofetal ED-B** -containing **fibronectin**: implications of production by both tumor and endothelial cells.
AUTHOR: Midulla M; Verma R; Pignatelli M; Ritter M A; Courtenay-Luck N S; George A J
CORPORATE SOURCE: Department of Immunology, Imperial College School of Medicine, Hammersmith Hospital, London, United Kingdom.
SOURCE: CANCER RESEARCH, (2000 Jan 1) 60 (1) 164-9. Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000204

AB **ED-B fibronectin** (**FN**) is a **FN isoform** derived from alternative splicing of the primary transcript of a single gene. Its expression on tumor stroma and neoformed tumor vasculature and its absence, with few exceptions, in normal adult tissues imply a prognostic and diagnostic value for **ED-B FN**. We investigated the location and source of **ED-B FN** because this will be of importance both in understanding its role in tumor development and in designing strategies to target this molecule. We have confirmed that **ED-B**

FN is expressed in the majority of breast and colorectal carcinoma tissue samples, with strong immunohistochemical staining around the tumor cells and in the tumor stroma. No staining of tumor neovasculature was seen. **ED-B FN** is produced by a range of tumor and endothelial (both primary and transformed) cell lines, as detected by reverse transcription-PCR, but is not expressed at the plasma membrane. Strong expression of human **ED-B FN** is seen in tumor xenografts. These data indicate that neoplastic cells can act as the source of **ED-B FN** in tumors. The lack of cell surface expression on tumor cell lines has clear implications for the design of therapeutic strategies which target this molecule.

L13 ANSWER 9 OF 52 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000042086 MEDLINE
DOCUMENT NUMBER: 20042086 PubMed ID: 10576667
TITLE: Distribution of laminin and **fibronectin isoforms** in oral mucosa and oral squamous cell carcinoma.
AUTHOR: Kosmehl H; Berndt A; Strassburger S; Borsi L; Rousselle P; Mandel U; Hyckel P; Zardi L; Katenkamp D
CORPORATE SOURCE: Institute of Pathology, Friedrich Schiller University, Jena, Germany.
SOURCE: BRITISH JOURNAL OF CANCER, (1999 Nov) 81 (6) 1071-9. Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991207

AB The expression of laminin and **fibronectin isoforms** varies with cellular maturation and differentiation and these differences may well influence cellular processes such as adhesion and motility. The basement membrane (BM) of **fetal** oral squamous epithelium contains the laminin chains, alpha2, alpha3, alpha5, beta1, beta2, beta3, gamma1 and gamma2. The BM of adult normal oral squamous epithelium comprises the laminin chains, alpha3, alpha5, beta1, beta3, gamma1 and gamma2. A re-expression of the laminin alpha2 and beta2 chains could be shown in adult hyperproliferative, dysplastic and carcinomatous lesions. In dysplasia and oral squamous cell carcinoma (OSCC), multifocal breaks of the BM are present as indicated by laminin chain antibodies. These breaks correlate to malignancy grade in their extent. Moreover, in the invasion front the alpha3 and gamma2 chain of

laminin-5 can immunohistochemically be found outside the BM within the cytoplasm of budding carcinoma cells and in the adjacent stroma. The correlation between the morphological pattern of invasive tumour clusters and a laminin-5 immunostaining in the adjacent stroma may suggest, first, that a laminin-5 deposition outside the BM is an immunohistochemical marker for invasion and second, that OSCC invasion is guided by the laminin-5 matrix. Expression of **oncofetal fibronectins** (IIICS de novo glycosylated **fibronectin** and **ED-B fibronectin**) could be demonstrated throughout the stromal compartment. However, the **ED-B fibronectin** synthesizing cells (RNA/RNA in situ hybridization) are confined to small stroma areas and to single stroma and inflammatory cells in the invasion front. A correlation of the number of **ED-B fibronectin** synthesizing cells to malignancy grade could not be seen. **ED-B fibronectin** mRNA-positive cells seem to be concentrated in areas of fibrous stroma recruitment with a linear alignment of stromal fibro-/myofibroblasts (desmoplasia). Double staining experiments (**ED-B fibronectin** in situ hybridization and alpha-smooth muscle actin immunohistochemistry) indicated that the stroma myofibroblasts are a preferential source of **ED-B fibronectin**. In conclusion, in OSCC, a **fetal** extracellular matrix conversion is demonstrable. Tumour cells (laminin alpha2 and beta2 chain) and recruited stromal myofibroblasts (**oncofetal ED-B fibronectin**) contribute to the **fetal** extracellular matrix milieu.

L13 ANSWER 10 OF 52 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999216534 MEDLINE
DOCUMENT NUMBER: 99216534 PubMed ID: 10196121
TITLE: NMR structure of the human **oncofoetal fibronectin ED-B** domain, a specific marker for angiogenesis.
AUTHOR: Fattorusso R; Pellecchia M; Viti F; Neri P; Neri D; Wuthrich K
CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik, Eidgenossische Technische Hochschule Honggerberg, CH-8093 Zurich, Switzerland.
SOURCE: STRUCTURE WITH FOLDING & DESIGN, (1999 Apr 15) 7 (4) 381-90.
Journal code: DEB; 100889329. ISSN: 0969-2126.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-2FNB

ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990618
Last Updated on STN: 20000407
Entered Medline: 19990610

AB BACKGROUND: The process of angiogenesis (i.e. the formation of new blood vessels from pre-existing ones) is fundamental to physiological processes such as reproduction, development and repair, as well as to pathological conditions such as tumor progression, rheumathoid arthritis and ocular disorders. The **oncofoetal ED-B** domain, a specific marker of angiogenesis, consists of 91 amino acid residues that are inserted by alternative splicing into the **fibronectin** (**FN**) molecule. RESULTS: The NMR structure of the **ED -B** domain is reported and reveals important differences from other **FN** type III domains. A comparison of the **ED-B** domain with the crystal structure of a four-domain **FN** fragment shows the novel features of **ED-B** to be located in loop regions that are buried at interdomain interfaces, and which therefore largely determine the global shape of the **FN** molecule. The negatively charged amino acids in this highly acidic protein are uniformly distributed over the molecular surface, with the sole exception of a solvent-exposed hydrophobic patch that represents a potential specific recognition site. Epitope mapping with 82 decapeptides that span the **ED-B** sequence revealed that three **ED-B**-specific monoclonal antibodies, which selectively target newly forming blood vessels in tumor-bearing mice, bind to adjacent regions on the **ED-B** surface. CONCLUSIONS: The NMR structure enables the identification of a large surface area of the **ED-B** domain that appears to be accessible in vivo, opening up new diagnostic and therapeutic opportunities. Furthermore, the mapping of specific monoclonal antibodies to the three-dimensional structure of the **ED-B** domain, and their use in angiogenesis inhibition experiments, provides a basis for further investigation of the role of the **ED-B** domain in the formation of new blood vessels.

L13 ANSWER 11 OF 52 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000440330 MEDLINE
DOCUMENT NUMBER: 20426121 PubMed ID: 10972305
TITLE: Characterization of the expression of the alternative splicing of the ED-A, **ED-B** and V regions of **fibronectin** mRNA in bovine ovarian follicles and corpora lutea.
AUTHOR: De Candia L M; Rodgers R J
CORPORATE SOURCE: Department of Medicine, Flinders University of South Australia, Australia.

SOURCE: REPRODUCTION, FERTILITY, AND DEVELOPMENT, (1999) 11 (6) 367-77.
Journal code: RAI; 8907465. ISSN: 1031-3613.
PUB. COUNTRY: Australia
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF136453
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000921

AB **Fibronectin** is an extracellular matrix glycoprotein. Alternative splicing of **fibronectin** mRNA within three specific regions, the extra domains (ED) A and B and the variable (V) or IIICS region, result in the production of different **isoforms** of **fibronectin**. These **isoforms** differentially regulate tissue developmental processes, such as those occurring during follicular and luteal development. The specific **isoforms** of **fibronectin** present in follicles and corpora lutea have not been identified. To identify these, primers for reverse transcription polymerase chain reaction (RT-PCR) were designed to the known bovine amino acid sequence of exons flanking the ED-A, **ED-B** and V regions. PCR products from bovine **fetal** liver cDNA were determined to be bovine **fibronectin** by the correct product size and DNA sequence homology to other species, and to the known bovine amino acid sequence. Bovine ovarian follicles (0.5-9 mm diameter) and corpora lutea (cyclic, early to late mid-luteal phase) were shown to express ED-A+, ED-A-, **ED-B**+, **ED-B**-, V+ and V **fibronectin isoforms**, similar to the liver, lung and kidney of fetuses, but generally not of adult animals. Thus follicles and corpora lutea express **isoforms** of **fibronectin** usually expressed in developing tissues.

L13 ANSWER 12 OF 52 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1999310639 MEDLINE
DOCUMENT NUMBER: 99310639 PubMed ID: 10381513
TITLE: A high-affinity human antibody that targets tumoral blood vessels.
AUTHOR: Tarli L; Balza E; Viti F; Borsi L; Castellani P; Berndorff D; Dinkelborg L; Neri D; Zardi L
CORPORATE SOURCE: Institut fur Molekularbiologie und Biophysik, ETH Honggerberg, Zurich, Switzerland.
SOURCE: BLOOD, (1999 Jul 1) 94 (1) 192-8.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990723

AB Angiogenesis is a characteristic feature of many aggressive tumors and of other relevant disorders. Molecules capable of specifically binding to new-forming blood vessels, but not to mature vessels, could be used as selective vehicles and would, therefore, open diagnostic and therapeutic opportunities. We have studied the distribution of the **ED-B oncofetal** domain of **fibronectin**, a marker of angiogenesis, in four different tumor animal models: the F9 murine teratocarcinoma, SKMEL-28 human melanoma, N592 human small cell lung carcinoma, and C51 human colon carcinoma. In all of these experimental models we observed accumulation of the **fibronectin isoform** containing the **ED-B** domain around neovascular structures when the tumors were in the exponentially growing phase, but not in the slow-growing phase. Then we performed biodistribution studies in mice bearing a subcutaneously implanted F9 murine teratocarcinoma, using a high-affinity human antibody fragment (L19) directed against the **ED-B** domain of **fibronectin**. Radiolabeled L19, but not an irrelevant anti-lysozyme antibody fragment (D1.3), efficiently localizes in the tumoral vessels. The maximal dose of L19 accumulated in the tumor was observed 3 hours after injection (8.2% injected dose per gram). By virtue of the rapid clearance of the antibody fragment from the circulation, tumor-to-blood ratios of 1.9, 3.7, and 11.8 were obtained at 3, 5, and 24 hours, respectively. The tumor-targeting performance of L19 was not dose-dependent in the 0.7 to 10 microg range of injected antibody. The integral of the radioactivity localized in tumoral vessels over 24 hours was greater than 70-fold higher than the integral of the radioactivity in blood over the same time period, normalized per gram of tissue or fluid. These findings quantitatively show that new-forming blood vessels can selectively be targeted in vivo using specific antibodies, and suggest that L19 may be of clinical utility for the immunoscintigraphic detection of angiogenesis in patients.

L13 ANSWER 13 OF 52 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1999359590 MEDLINE
DOCUMENT NUMBER: 99359590 PubMed ID: 10398159
TITLE: Expression of EDA/**EDB isoforms** of **fibronectin** in papillary carcinoma of the thyroid.
AUTHOR: Scarpino S; Stoppacciaro A; Pellegrini C; Marzullo A;

Zardi L; Tartaglia F; Viale G; Ruco L P
CORPORATE SOURCE: Dipartimento di Medicina Sperimentale e Patologia, Universita 'La Sapienza', Roma, Italy.
SOURCE: JOURNAL OF PATHOLOGY, (1999 Jun) 188 (2) 163-7.
Journal code: JLB; 0204634. ISSN: 0022-3417.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000314
Last Updated on STN: 20000314
Entered Medline: 20000229

AB Cellular **fibronectins** containing the extracellular domain A or B (EDA and **EDB**) are particularly abundant in **fetal** and neoplastic tissues. The presence of EDA and **EDB** was investigated in 28 cases of papillary carcinoma of the thyroid using IST-9 and BC-1 monoclonal antibodies. Immunostaining for EDA and **EDB** was detected in tumour stroma, in tumour basement membranes, and in tumour blood vessels. EDA was present in 27 of the 28 cases, in 20 of which more than 75 per cent of the tumour stroma was stained. Immunostaining for **EDB** was detected in 23 of the 28 cases and was less pronounced than that for EDA, being present in less than 25 per cent of the tumour stroma in most cases. Reactivity for EDA/**EDB** was not observed in the adjacent normal thyroid in any of the cases investigated. In a group of 20 non-papillary tumours, immunostaining for EDA was present in the stroma of three follicular carcinomas (one minimally and two widely invasive), one medullary carcinoma, and 5 of 16 follicular adenomas; expression of **EDB** was more restricted, being present in only the two cases of widely invasive follicular carcinoma. The presence of EDA and **EDB** was not correlated with the extent of fibrosis or the degree of tumour cell differentiation. Immunoreactivity was already present in microcarcinomas. These observations raise the possibility that the production of **oncofetal fibronectins** is an important step in papillary carcinoma tumourigenesis, perhaps facilitating adhesion and spreading of tumour cells.

L13 ANSWER 14 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1999:161891 SCISEARCH
THE GENUINE ARTICLE: 168DA
TITLE: Detection of multiple **fibronectin** **isoforms** in **fetal** fibroblast monolayer culture: a novel method for the qualitative and quantitative detection of multiple antigens

Searcher : Shears 308-4994

AUTHOR: Zijlstra A; Schelling M E (Reprint)
CORPORATE SOURCE: WASHINGTON STATE UNIV, DEPT GENET & CELL BIOL, PULLMAN, WA 99164 (Reprint); WASHINGTON STATE UNIV, DEPT GENET & CELL BIOL, PULLMAN, WA 99164
COUNTRY OF AUTHOR: USA
SOURCE: HISTOCHEMISTRY AND CELL BIOLOGY, (FEB 1999) Vol. 111, No. 2, pp. 163-169.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0301-5564.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 15

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Analyzing the expression of multiple distinct antigens within a single monolayer culture involves cumbersome immunostaining techniques. We describe a simple and economical procedure for the detection and quantification of multiple antigens within a single monolayer. By generating an immunohistochemical grid which divides a monolayer in a standard tissue culture dish into 20 distinct areas, we were able to detect and quantify four individual **fibronectin** (**FN**) **isoforms** within a single fibroblast monolayer culture. Quantification of each **isoform** was performed using a modified enzyme-linked immunoassay. In addition, within the same monolayer, each **FN isoform** was detected using standard immunohistochemical detection with DAB visualization. Using this novel approach to immunohistochemical analysis we determined that within the first 4 days of culture, the quantity of all **FN isoforms** increases faster than the number of cells. However, upon reaching confluency, the quantity of **FN**/cell drops dramatically. After reaching confluency, the amount of **FN**/cell levels off and remains constant within the postconfluent monolayer. Statistical analysis of the quantity of **FN**/cell indicates that a significant reduction in the amount of **FN**/cell occurs in the 2 days prior to reaching confluency. The distribution of all the **FN isoforms**, with the exception of B-**FN**, was found along the length of the cell body. In contrast, the distribution of B-**FN** was altered in postconfluent monolayers where it was detected only in distinct locations within the monolayer.

L13 ANSWER 15 OF 52 SCISEARCH COPYRIGHT 2001 ISI (R)
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The splicing variant of **fibronectin** containing the **ED-B** domain (**oncofoetal fibronectin**) occurs in **foetal** tissues, reparative processes, organ fibrosis and in tumour tissues. Consequently, a supportive effect of ED-Bt **fibronectin** for tissue remodelling and tumour progression is assumed. A non-radioactive RNA-RNA in situ hybridization protocol for the investigation of **ED-B+ fibronectin** synthesis applicable in human tissues is introduced. The **ED-B+ fibronectin** synthesis was investigated in human disease processes, for which the occurrence of **ED-B+ fibronectin** is well demonstrated by immunohistochemistry (rheumatoid arthritis, oral squamous cell carcinoma, invasive ductal carcinoma of the breast and nodular palmar fibromatosis). The **ED-B+ fibronectin** synthesis could be shown in lining cells and in endothelial cells of synovial villi in rheumatoid arthritis, in stromal cells of oral squamous cell carcinoma and invasive ductal carcinoma and in fibro-/myofibroblasts in the proliferative and early involutional phase of nodular palmar fibromatosis. By means of double labelling (alpha-smooth muscle actin immunostaining - **ED-B+ fibronectin** in situ hybridization), the **ED-B+ fibronectin** synthesis could be shown to be a typical feature of myofibroblasts. In contrast to the often diffuse **ED-B+ fibronectin** immunostaining, only a few synthetically active stromal cells were observed focally accentuated within the tumour, which were interpreted as hot spots of tumour-stroma interaction.